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CLINICAL VARIATIONS IN THE DIAGNOSIS OF PSITTACOSIS*

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SINCE the relaxation of regulations governing the transportation and sale of psittacine birds in December, 1951, there has been a dramatic increase in the number of human infections with psittacosis virus.[1-5] Recognition of these infections requires an awareness of the importance of avian contact and knowledge of the clinical characteristics of psittacosis. Excellent summaries of the clinical and epidemiologic features of psittacosis are available in a number of textbooks and articles,[6-8] so that an extensive review of the disease is unnecessary. Certain problems in diagnosis and treatment, however, deserve continued emphasis.

The clinical manifestations of psittacosis are extremely variable. Infection with psittacosis virus may result in severe, and sometimes fatal, disease or it may induce only a mild or subclinical illness. Psittacosis may pursue a prolonged low-grade course, or it may be of short duration, terminating abruptly. It may simulate a variety of infectious diseases such as Q fever, influenza, and infectious mononucleosis, and such noninfectious diseases as neoplasms of the lung, sarcoidosis and rheumatic fever. The purpose of this paper is to describe the clinical variations observed in a series of patients with psittacosis and to illustrate some of the problems presented in differential diagnosis.

SUMMARY OF CASES

Clinical Features

Table 1 shows the epidemiologic, clinical and laboratory findings in 13 cases of psittacosis diagnosed at University Hospitals of Cleveland between April, 1949, and January, 1954. All the patients were adults. Nine were white, and 4 were Negro. Seven patients were exposed to parakeets, 5 were exposed to pigeons, and 1 had no known exposure to birds.

Four of the patients had severe illnesses (SL-735, SL-1385, SL-1691 and SL-987). Eight patients had moderately severe illnesses, and 1 case was extremely mild (M-598). Chills were not uncommon, shaking chills occurring in 5 cases. Cough occurred in 12 cases; 4 of these patients had hemoptysis. Dyspnea was present in 3, and chest pain in 2 cases. Delirium occurred in 2. The chief complaint in 1 case was nausea, vomiting and abdominal pain (SL-1691). One patient had epistaxis. The other major symptoms were primarily systemic.

Physical examination of the chest resulted in a wide variation of findings, ranging from normal to signs of marked consolidation. Other abnormal physical findings were noted, delirium and stupor occurring in 1 case (SL-735), and hepatosplenomegaly in 2 (SL-738 and SL-1691). One of the patients with hepatosplenomegaly had acute thyroiditis and exudative tonsillitis in addition (SL-1691). Abnormal laboratory findings included leukopenia and leukocytosis in 3 cases each and an elevated cold-hemagglutinin titer in 1 case.

The degree of pulmonary involvement demonstrated on the roentgenograms varied from increased bronchovascular markings to widespread infiltration throughout both lungs. In most cases, the extent of infiltration was minimal or moderate; bronchopneumonia was present in 9 cases, and lobar consolidation in 2 (SL-1735 and SL-987).

Diagnosis

Problems arising in differential diagnosis were common. Primary atypical pneumonia was the syndrome most frequently considered. Bacterial pneumonia, influenza, acute bronchitis, meningitis, encephalitis, typhoid fever, brucellosis, infectious hepatitis, infectious mononucleosis, subacute bacterial endocarditis, rheumatic fever, carcinoma of the lung and sarcoidosis were other diseases listed in differential diagnosis.

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Serum samples drawn in the acute (twelve days or less) and convalescent phases (more than twelve days) from 11 patients were examined in a complement-fixation test,[1] using purified Lygranum antigen, for the presence of antibodies to the psittacosis-lymphogranuloma group of viruses. Titer is expressed as the reciprocal of the highest dilution of serum causing complete fixation of complement. A fourfold or greater rise in titer was observed in 11 cases, an eightfold or greater increase occurring in 10 of these. From 2 patients, the initial serum was obtained during the convalescent stage of illness, and both had elevated antibody titers; serum subsequently obtained from 1 showed an eightfold fall in titer.

Antibiotic treatment included the administration of chlortetracycline in 5 cases; chlortetracycline and penicillin in 1 case; chlortetracycline, penicillin and streptomycin in 1 case; oxytetracycline and penicillin in 1 case; penicillin in 2 cases; and sulfonamides in 1 case. Two patients received no specific treatment. The temperature returned to normal within forty-eight hours in 6 of the 8 cases in which tetracyclines were used.

Case Reports

The following cases illustrate some of the clinical variations of psittacosis and the resulting diagnostic problems.

Table 1. *Major Clinical Features in Thirteen Patients with Psittacosis.*

Case No.	Age	Sex	Race	Occupation	Bird Exposure	Place of Exposure	Symptoms*										
							Myalgia	Shaking Chills	Dyspnea	Cough	Hemoptysis	Chest Pain	Epistaxis	Abdominal Pain	Delirium	Stupor	Duration of Fever
	yr.																days
SL-733	44	F	N	Housewife	Pigeons	Home	+	0	0	+	0	+	0	0	0	0	10
SL-735	46	F	N	Housewife	Pigeons	Home	+	0	+	+	+	0	0	0	+	+	11
SL-738	25	M	N	Laborer	Pigeons	Home	+	0	0	+	0	0	0	0	0	0	5
M-598	62	F	N	Housewife	Pigeons	Home	0	0	0	+	0	0	0	0	0	0	0
SL-1385	62	F	W	Housewife	Pigeons	Yard	0	0	+	+	+	0	0	0	0	0	9
SL-1666	38	M	W	Salesman	Parakeet	Home	+	+	0	0	0	0	0	0	0	0	8
SL-1691	31	F	W	Housewife	Parakeet	Home	+	0	0	+	0	+	0	+	0	0	14
SL-1695	43	M	W	Railway-express messenger	Parakeets	Express cars	0	+	0	+	0	0	+	0	0	0	7
SL-1698	67	M	W	Manager of stamp agency	Parakeets	Restaurant	0	0	0	+	+	0	0	0	0	0	—
SL-1735	30	F	W	Housewife	Parakeets	Home	0	+	0	+	0	0	0	0	0	0	7
M-1143	44	M	W	Railway-express messenger	Parakeets	Express cars	+	+	0	+	0	0	0	0	0	0	5
SL-1898	52	F	W	Housewife	Parakeet	Home	+	0	0	+	0	0	0	0	0	0	7
SL-987	51	F	W	Housewife	——	——	0	+	+	+	+	0	0	0	+	0	14

Case No.	Severity
SL-733	Moderate
SL-735	Severe
SL-738	Moderate
M-598	Mild
SL-1385	Severe
SL-1666	Moderate
SL-1691	Severe
SL-1695	Moderate
SL-1698	Moderate
SL-1735	Moderate
M-1143	Moderate
SL-1898	Moderate
SL-987	Severe

*0=absent; +=present; −=unknown.
†When leukocytosis or leukopenia occurred, highest or lowest figures recorded; in other cases, white-cell count obtained on admission used.

Case 1 (SL-1666) (Fig. 1). A 38-year-old man noted the onset of coryza and generalized oppressive headache 5 days before admission. On the following day anorexia, malaise and fever developed. Three days before admission the headache became severe and there was pain on rotation or flexion of the neck. There was also pain in the upper thoracic spine and in both flanks. The patient had a parakeet at home, and he had cleaned the bird cage approximately 2 weeks before the onset of this illness.

Examination showed an acutely ill lethargic white male with marked tenderness of the sternocleidomastoid muscles and of the muscles of the posterior cervical region. There was pain on motion of the neck, but no nuchal rigidity. The chest was clear to percussion and auscultation. There was considerable spasm and tenderness of the paraspinal musculature and tenderness in the right flank.

The temperature was 103.8°F. (39.9°C.), the pulse 96, and the respirations 24. The blood pressure was 116/82.

The white-cell count was 3600, with 59 per cent segmented and 3 per cent unsegmented neutrophils, 32 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. On the following day the white-cell count was 2700. Lumbar puncture on admission was normal. Throat and stool cultures showed no pathogenic bacteria. Blood culture revealed no growth. Initial roentgenograms of the chest showed a poorly defined area of increased haziness in the left-middle-lung field. A repeat roentgenogram of the chest 2 days later showed an increase in the infiltrative process.

TABLE 1 *(Concluded).*

CASE NO.	SIGNS*					TREATMENT	NORMAL TEMPERATURE WITHIN 48 HR.	LABORATORY FINDINGS			
	CONSOLIDATION	RALES	HEPATOMEGALY	SPLENOMEGALY	INFILTRATION ON CHEST ROENTGENOGRAM	ANTIBIOTIC		WHITE-CELL COUNT† x10³	COLD-AGGLUTININ TITER	DAY OF DISEASE	COMPLEMENT FIXATION WITH LYGRANUM
SL-733	0	0	0	0	Minimal	Sulfamerazine } Sulfadiazine }	No	10.5	256	10 31	8 64
SL-735	0	+	0	0	Minimal	Chlortetracycline	Yes	16.6	<4	9 20	64 512
SL-738	0	+	+	+	Moderate	Chlortetracycline	Yes	11.8	<4	4 25	<16 128
M-598	—	—	—	—	——	None	—	—	—	−7 83	< 8 128
SL-1385	0	+	0	0	Moderate	Penicillin } Streptomycin }	No	8.8	<4	8	< 4
						Chlortetracycline	Yes			19	64
SL-1666	+	+	0	0	Moderate	Chlortetracycline	Yes	2.5	<4	5 43	< 4 128
SL-1691	0	0	+	+	Minimal	Penicillin	Yes	3.2	—	16 31	32 64
SL-1695	0	+	0	0	Minimal	Chlortetracycline	Yes	5.4	—	7 22	< 4 512
SL-1698	+	+	0	0	Moderate	None	—	8.8	<4	28 16 mo.	128 16
SL-1735	+	+	0	0	Extensive	Penicillin	No	7.3	<4	4	< 4
						Chlortetracycline	No			12	128
M-1143	0	0	0	0	——	Penicillin	No	—	—	8	32
						Oxytetracycline	Yes			18	512
SL-1898	+	+	0	0	Moderate	Chlortetracycline	No	7.5	<4	5 14	< 4 16
SL-987	+	+	0	0	Extensive	Penicillin	No	3.6	<4	8	8
						Placebo	No			18	64

*0 = absent; + = present; − = unknown.

†When leukocytosis or leukopenia occurred, highest or lowest figures recorded; in other cases, white-cell count obtained on admission used.

The patient had a shaking chill, with a temperature spike to 104.9°F. (40.5°C.) 24 hours after admission. On the 2d hospital day chlortetracycline, 250 mg. every 4 hours, was started, and the temperature fell to normal limits within 30 hours. On the following day, dullness to percussion, diminished breath sounds, egophony, pectoriloquy and medium fine rales were noted over a small area at the inferior border of the left scapula. Subsequently, the physical findings in the chest cleared progressively, and on the 10th hospital day a roentgenogram of the chest showed almost complete resolution of the pneumonia. The complement-fixation titer was < 4 on the 5th and 128 on the 43d day of illness.

The meningismus and marked spasm and tenderness of the paraspinal musculature on admission suggested the diagnosis of poliomyelitis. The spiking fever, relatively slow pulse and leukopenia suggested typhoid fever. Abnormal physical findings in the chest were not present at the time of admission and did not develop until three days later. The patient had a good response to chlortetracycline therapy.

CASE 2 (SL-1691) (Fig. 2). A 31-year-old housewife had intermittent crampy pain in the middle and right lower quadrants of the abdomen 9 days before admission. On the following day nausea, vomiting, frequent retching, feverishness and headache appeared. The nausea, vomiting and retching slowly subsided, but the feverishness and headache continued until admission. Four days before admission she noted an occasional nonproductive cough associated with twinges of pain in the right lower aspect of the chest. She had acquired a cockatoo 6 months and a parakeet 1 month previously.

Physical examination showed a woman who appeared acutely ill. The tonsils were hyperemic. The lungs were clear to percussion and auscultation. There was tenderness in the periumbilical area and in the right lower quadrant, but there was no evidence of muscle spasm, masses or palpable organs.

The temperature was 101.1°F. (38.4°C.), the pulse 100, and the respirations 22. The blood pressure was 140/100.

Examination of the blood revealed a white-cell count of 6150, with 55 per cent segmented and 11 per cent unsegmented neutrophils, 18 per cent lymphocytes and 16 per cent monocytes. The white-cell count was 3200 on the 3d hospital day. A throat culture disclosed no pathogenic bacteria. Two blood cultures showed no growth. Typhoid O and H, paratyphoid A and B, and *Brucella abortus* agglutinins were absent at a dilution of 1:20. The heterophil-antibody agglutination titer was 1:32. Initial roentgenograms of the chest showed heavy pulmonary vascular markings bilaterally with an ill defined area of density in the region of the right 2d rib anteriorly.

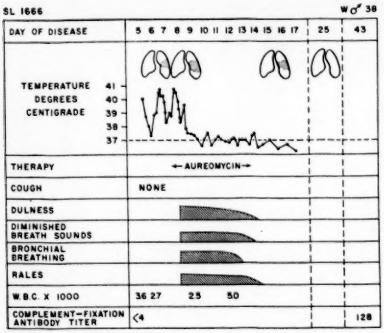

FIGURE 1. *Moderately Severe Case of Psittacosis in Which Shaking Chills, Severe Generalized Myalgia and Meningismus Occurred.*

On the 1st hospital day an acute exudative tonsillitis developed on the left, with an enlarged and tender tonsillar lymph node. The liver was palpated 2 cm. below the right costal margin. No rash, icterus or palpable spleen was present at this time. Two days later a bilateral pharyngitis was observed, and the anterior cervical and axillary lymph nodes were enlarged and acutely tender. Aqueous procaine penicillin was started intramuscularly on the 3d hospital day, and this treatment was continued until the day of discharge. On the 5th hospital day, though the temperature had fallen to normal, splenomegaly was noted, and the isthmus of the thyroid gland had become acutely tender. A repeat roentgenogram of the chest continued to show prominent markings in the region of the right 2d rib. At the time of discharge on the 8th hospital day the tip of the spleen was still palpable and the thyroid isthmus remained tender. The complement-fixation titer of the patient's serum against Lygranum antigen was 32 on the 16th and 64 on the 31st day of illness.

This case of psittacosis was associated with exudative tonsillitis, leukopenia, pulmonary infiltration, hepatosplenomegaly and acute thyroiditis. Subacute bacterial endocarditis, rheumatic fever, brucellosis, infectious mononucleosis and typhoid fever were all entertained in differential diagnosis.

CASE 3 (SL-735) (Fig. 3). A 46-year-old Negress noted gradual onset and progression of anorexia, severe headache, marked photophobia and extreme weakness over an 8-day period. Three days before admission she became disoriented, and the temperature rose to 103°F. (39.4°C.). She became more disoriented during the following 3 days and a cough productive of small amounts of blood-tinged sputum developed. She was a member of a household where pigeons were being raised in the basement,[1] and had made frequent trips to the basement to do her laundry.

Physical examination revealed an obese, critically ill woman in a semistuporous state with many athetoid movements of the arms and legs. There was generalized muscle irritability, but there were no persistent muscle spasms. The lungs showed slight dullness to percussion and diminished breath sounds over the right lower lobe. No rales were heard.

The temperature was 101.8°F. (38.8°C.), the pulse 135, and the respirations 30. The blood pressure was 220/138.

The white-cell count was 11,900, with 75 per cent segmented and 6 per cent unsegmented neutrophils, 15 per cent monocytes, 3 per cent lymphocytes and 1 per cent eosinophils. Urinalysis showed a ++ test for albumin. Throat and sputum cultures revealed no pathogenic bacteria. Lumbar puncture was normal. Initial roentgenograms of the chest showed increased bronchovascular markings in the region of the right base.

During the 1st 24 hours after admission the patient became progressively more stuporous and could not be aroused. In view of this, chlortetracycline, 1 gm. every 6 hours, was begun. Twenty-four hours later she was fully responsive and well oriented, and the temperature was falling toward normal. On the 11th hospital day a roentgenogram of the chest showed a slight decrease in the prominence of the bronchovascular markings at the right base. The complement-fixation titer of the serum was 64 on the 9th and 512 on the 20th day of illness.

This patient gave signs of encephalitis with the development of delirium followed by stupor. Respiratory symptoms were minor, and there was minimal pulmonary infiltration. The clinical response to chlortetracycline therapy was good.

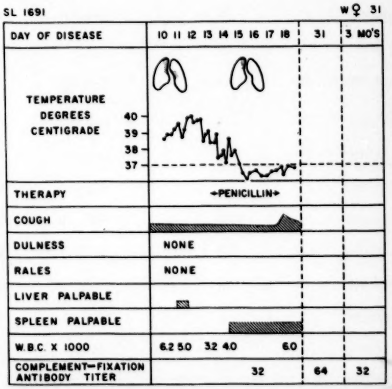

FIGURE 2. *Severe Case of Psittacosis in Which Hepatosplenomegaly, Acute Thyroiditis, Exudative Tonsillitis and Leukopenia Occurred.*

CASE 4 (SL-1385) (Fig. 4). A 62-year-old woman was admitted to the hospital complaining of fever, malaise and chilliness of 4 days' duration. She had had no chest pain or cough.

Physical examination showed an acutely ill woman in marked respiratory distress. There was splinting of the right lower costal border. The lungs revealed dullness to percussion, decreased tactile fremitus and diminished breath sounds over the right lower lobe posteriorly. No rales were heard. The abdomen was moderately distended.

The temperature was 104.9°F. (40.5°C.), the pulse 104, and the respirations 32. The blood pressure was 120/90.

Laboratory studies showed a white-cell count of 8800, with 77 per cent segmented and 10 per cent unsegmented neutrophils. Throat culture and 2 sputum cultures disclosed no pathogenic bacteria. Blood culture was sterile. A roentgenogram of the chest showed a few hazy shadows above the right dome of the diaphragm interpreted as a small area of pneumonic infiltration with atelectasis.

The patient was immediately started on penicillin, streptomycin and oxygen therapy. During the 1st 3 hospital days her condition was critical. Three days after admission she began to cough up tenacious bloody sputum. At this time penicillin and streptomycin were discontinued, and chlortetracycline was started. Two days later the temperature had fallen to normal. Acid-fast stains, acid-fast cultures and 8 Papanicolaou examinations of the sputum were negative. The cold-hemagglutinin titers of serum samples from acute and convalescent phases were not elevated.

Examination of the chest on the 10th hospital day continued to show dullness to percussion, decreased tactile fremitus, diminished breath sounds and coarse rales at the right base posteriorly. A repeat roentgenogram of the chest on the following day showed incomplete clearing of the pneumonic process. In view of the unusual aspects of the illness, bronchoscopy was performed on the 15th hospital day to rule out the possibility of adenoma or carcinoma of the bronchus. Bronchoscopic examination revealed no tumor, but inflammatory changes of acute bronchitis were present. Bronchial washings were negative for tumor cells. At the time of discharge on the 17th hospital day a few fine rales were still present, and roentgenograms of the

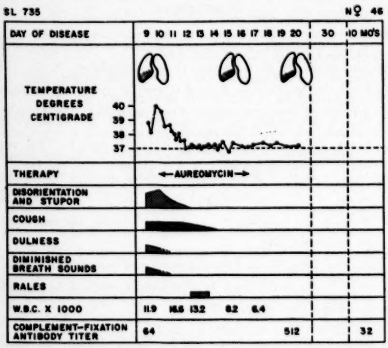

FIGURE 3. *Severe Case of Psittacosis with Signs of Encephalitis.*

chest continued to show incomplete resolution of the patchy infiltrate at the right base. The complement-fixation titer of the patient's serum against Lygranum antigen was < 4 on the 8th and 64 on the 19th day of illness. She had been accustomed to feeding pigeons in her yard.

Hemoptysis, a slowly resolving pneumonia and physical and roentgenologic findings of bronchial obstruction strongly suggested the diagnosis of carcinoma of the lung in this sixty-two-year-old woman.

CASE 5 (M-598). A 62-year-old Negress had a mild cough and slight malaise a few days after she had blood drawn for study of an outbreak of psittacosis in her home. She, too, was a member of the household where pigeons were being raised in the basement. Her illness was mild, and she stayed in bed for 1 day. The complement-fixation titer of serum drawn before the illness was < 8. Three months later the titer was 128.

Although the symptoms in this case were mild, the infection provoked an excellent antibody response.

DISCUSSION

Table 1 summarizes the variety of clinical manifestations noted in 13 patients with psittacosis. Five case reports have been presented in some detail to illustrate certain of these variations. Psittacosis infection simulated a variety of diseases ranging from acute bronchitis to lobar pneumonia; it mimicked poliomyelitis and encephalitis; it had to be distinguished from carcinoma of the lung.

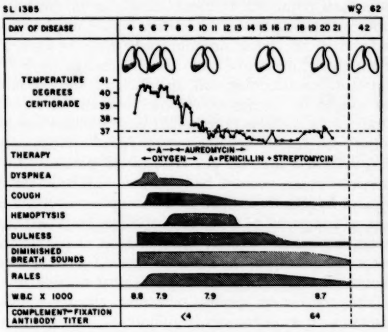

FIGURE 4. *Severe Case of Psittacosis Simulating Carcinoma of the Lung.*

The severity of psittacosis varies within wide limits. Subclinical infections occur frequently, as emphasized in a previous paper.[1] Mild infections are also common, but often go unrecognized since they simulate common upper respiratory diseases. Moderately severe, severe and fatal infections are probably less frequent, although more commonly diagnosed because of hospitalization. The duration of clinical infection with psittacosis also varies. The duration may be short, terminating abruptly, or it may pursue a prolonged, low-grade course.

The clinical features of this disease show even greater variability. On physical examination of the chest, the presence of medium moist rales in the absence of consolidation is the most characteristic finding. It is not unusual, however, for abnormal chest findings to be absent or, in contrast, for consolidation to be present. Radiographic examinations of the chest also show striking differences in the extent and character of infiltration, although it is generally bronchopneumonic in type. In some patients other organs and systems are involved (Cases 1, 2 and 3). Symptoms and signs referable to the central nervous system occurred in 2 of the patients described above (Cases 1 and 3), and hepatosplenomegaly, acute thyroiditis and exudative tonsillitis in 1 (Case 2).

The severe cases of psittacosis show the greatest variability in clinical features. Encephalitic symptoms

may occur (Case 3); marked pulmonary and systemic symptoms may be seen (Case 4). In fatal cases pneumonia is widespread throughout both lungs. Cyanosis often appears early while the respirations remain unlabored. Extensive signs of consolidation develop, and pleural and pericardial friction rubs may appear.[2] In the terminal stages delirium and stupor set in, and death generally results from pulmonary insufficiency and generalized toxemia.[8]

For the differential diagnosis of psittacosis an appreciation of the great variability of the infectious process is required. Without knowledge of this variability the diagnosis of psittacosis would not be considered in the more unusual cases such as Case 2. Fortunately, history of bird contact is extremely helpful in differential diagnosis, and such a history should be sought in all obscure febrile illnesses. A recent study of 78 patients hospitalized with illnesses resembling psittacosis or primary atypical pneumonia demonstrated that 46 per cent of 26 patients with previous avian contact had elevated antibody titers against Lygranum antigen in the complement-fixation test, as compared to 4 per cent of 52 patients without avian exposure.[1] In all suspected cases of psittacosis serum samples from the acute and convalescent phases should be examined by the complement-fixation test.

The efficacy of specific treatment for a variable disease such as psittacosis is difficult to measure. Six of the 8 patients in the present report who were treated with chlortetracycline or oxytetracycline exhibited apparent responses to this therapy. There is a growing body of laboratory and clinical evidence that the tetracycline derivatives are effective in the treatment of psittacosis,[3,9-17] and these drugs are recommended as the antibiotics of choice for psittacosis. Tetracyclines are indicated in all patients, suspected clinically of having psittacosis, who give a history of exposure to birds.

Although effective measures have been developed for the treatment of psittacosis, problems in the prevention of this disease still exist. Since relaxation of interstate quarantine regulations in December, 1951, large numbers of parakeets have been shipped over long distances to many parts of the United States. They have frequently been shipped under overcrowded conditions with minimal care, resulting in the death of many birds. Such conditions are ideal for the spread of psittacosis to uninfected birds, many of which survive and become healthy carriers of the disease. These carriers represent potential sources of human infection in areas where they are shipped. Many recent reports[1-5] attest the danger inherent in parakeets and other birds as pets in the home. One of the patients with psittacosis described by Maclachlan et al.[2] showed a fulminating course and died about twenty hours after hospitalization. A similar fatal case, not included in this report, recently occurred in Cleveland.[18] Such a hazard suggests that regulation of the traffic and sale of psittacine birds should be reconsidered.

Summary and Conclusions

The clinical manifestations of a series of 13 patients with psittacosis are summarized, and the cases of 5 patients reported in detail to illustrate the variable features of this disease. With the increasing popularity of parakeets, the diagnosis of psittacosis must be considered in patients with obscure febrile illnesses, particularly if there is a history of exposure to psittacine birds and roentgenograms of the chest demonstrate pulmonary infiltration. The danger inherent in parakeets and other birds as pets in the home is emphasized.

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EFFECT OF VENOUS-SHUNT SURGERY ON LIVER FUNCTION IN PATIENTS WITH PORTAL HYPERTENSION*

A Follow-up Study of 125 Patients Operated on in the Last Ten Years

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ONE of the most encouraging developments in the treatment of liver disease in the past ten years has been the perfection of surgical technics that relieve portal hypertension and reduce the hazard of bleeding from esophageal varices. The most commonly advocated procedure is a venovenous anastomosis shunting blood from the portal into the systemic circulation.[1,2] We have had over ten years of experience at the Massachusetts General Hospital in attempting to relieve portal hypertension by venous-shunt surgery, and it is important now to assess the results of this therapy and to determine its effect on liver function.

The data presented are those resulting from the study of 125 patients who have had 130 technically completed shunt operations in the period from March, 1945, to November, 1954. All the survivors now living have been followed for at least twelve months, and the longest follow-up period is ten years. Esophageal varices were demonstrated by x-ray examination preoperatively in each patient, and this has been accepted as proof of the existence of portal hypertension. After the exclusion of other causes of upper gastrointestinal bleeding, the varices were considered to be the source of hemorrhage for which shunt surgery was indicated. The majority of these patients have been operated upon by one of us (R.R.L.), and they have all been followed personally by one or more of us.

TYPE OF SHUNT

Eighty-eight of these patients had a splenectomy and a splenorenal anastomosis (Table 1). The eventual mortality in this group was 21 deaths, or 24 per cent. Thirty-seven patients had a direct portacaval anastomosis, with a final mortality to date of 15 deaths, or 40.5 per cent.

In the splenorenal group a total of 10 patients, or 11 per cent, died of liver failure as compared to a total death of 10 patients, or 27 per cent, who died of liver failure after a portacaval shunt. This difference in mortality, as well as a similar morbidity in our patients after portacaval shunts, has made us prefer to do the splenorenal shunt when possible in spite of the fact that recurrent bleeding was slightly more frequent in the splenorenal group.

There were 5 so-called makeshift, or lesser, shunts. These shunts were anastomoses between lesser tributaries of the portal circulation and the inferior vena cava, the left adrenal vein and the left ovarian vein. These were made in patients in whom it was found impossible to utilize the portal vein or in those who had had previous splenectomies. In general, it is said that these shunts have limited value, and none of them are apt to be as satisfactory as a splenorenal or direct portacaval shunt.

TABLE 1. *Type of Venous-Shunt Procedure in 125 Patients with Portal Hypertension.*

TYPE OF OPERATION	TOTALS*	DEATHS
Splenorenal	88	21(23.8%)
Direct portacaval	37	15(40.5%)
Makeshift	5	1(20.0%)
Totals	130	37

*There were 5 more procedures than patients because 5 patients had 2 types of shunts constructed.

PATHOLOGICAL DIAGNOSIS (TABLE 2)

In assessing the effect of the operations on liver function, one should review the pathology in the liver at the time of operation. A wedge biopsy was obtained for histologic study in each patient. Nineteen patients had no demonstrable liver disease microscopically and are believed to have had extrahepatic portal-bed block as the cause of the portal hypertension. An additional patient whose biopsy was lost before it reached the Pathology Laboratory was clinically classified as having extrahepatic portal-bed block. A total of 98 patients had a portal type of cirrhosis, and these have been sub-classified as 20 of the alcoholic, 31 of the postnecrotic and 47 of the unclassified type. There were 4 patients with biliary cirrhosis and 3 with miscellaneous types of "hepatitis."

MORTALITY

The immediate operative mortality has been reported in detail,[3] and it will be sufficient to mention here that there were 14 operative deaths, representing an operative mortality of 11 per cent. Subsequently, 23 patients died. Of patients with normal livers, only 3 died, none of them from liver failure.

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This represents a mortality for this group of 16 per cent. In the patients with alcoholic cirrhosis there was a total mortality of 50 per cent. The postnecrotic group had a total mortality of 32 per cent, which does not bear out the widespread belief that this type of cirrhosis has a worse prognosis than other types.

TABLE 2. *Pathological Diagnoses at Operation in 125 Cases of Portal Hypertension.*

DIAGNOSIS	NO. OF CASES	NO. OF DEATHS
Normal liver	19	3(15.8%)
Portal cirrhosis	98	
Alcoholic type	20	10(50.0%)
Postnecrotic type	31	11(32.0%)
Unclassified	47	12(25.5%)
Biliary cirrhosis	4	1(25.0%)
Miscellaneous	3	
Sarcoid	1	0
Focal hepatitis	1	0
Chronic perihepatitis	1	0
No biopsy	1	0
Totals	125	37(29.0%)

There has been a 25.5 per cent mortality in the unclassified group to date. One out of 4, or 25 per cent, patients with biliary cirrhosis is dead, and there have been no deaths in the miscellaneous group. This,

TABLE 3. *Late Deaths after Shunt Surgery.*

CAUSE OF DEATH	PATIENTS WITH NORMAL LIVERS		PATIENTS WITH CIRRHOSIS		TOTALS
	SPLENO-RENAL ANASTOMOSIS	PORTA-CAVAL ANASTOMOSIS	SPLENO-RENAL ANASTOMOSIS	PORTA-CAVAL ANASTOMOSIS	
Liver failure			7	5	12
Hemorrhage from varices			2		2
Cardiovascular disease	1	1		4	6
Pulmonary disease	1				1
Renal disease				1	1
Intestinal obstruction			1		1

then, represents a total mortality over the ten-year period of 29 per cent.

In a review of the causes of late death (Table 3), it is interesting that only 12 of these patients died of liver failure, and only 2 from further esophageal bleeding; 6 died from cardiovascular disease, and 1 each from pulmonary disease, renal disease and intestinal obstruction.

SURVIVAL

At this time 82 patients are known to be alive and have been in direct communication with us in the last three months. Four have not been heard from in three, two, one and one years respectively. Two patients out of the group have been completely lost to follow-up study since operation.

Previously published results of Blakemore,[4] Linton[5] and Child[6] prove conclusively the effectiveness of this type of operation in preventing massive esophageal bleeding. One of the great questions that is still unanswered is whether or not this type of surgery significantly prolongs life beyond the first year after operation. As will be seen from the following data, we believe that it does do just this.

Figure 1 demonstrates the total number of patients with shunts completed and the total number of survivors in each of the successive years from 1945 through 1954. Thus, it is seen that out of 3 patients operated on ten years ago 2, or 66 per cent, are still living; of 54 operated on at least five years ago 27, or 50 per cent, are still living; and of 125 patients 102, or 81 per cent, lived for at least one year. It can also be seen from this chart that 111 patients, or 89 per

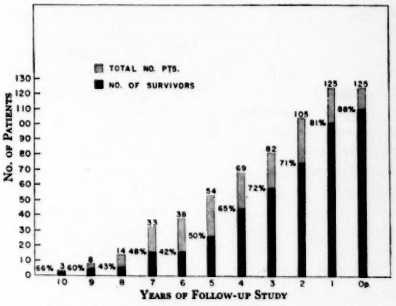

FIGURE 1. *Number of Patients Operated on and Number of Survivors One to Ten Years after Shunt Surgery. The column at the right represents 111 of 125 patients surviving the operative procedure.*

cent, survived operation, leaving 9 patients who died within the first twelve months after surviving operation. These data show without question a significant increase in survival in the first year after operation in these patients as compared to the previously reported survival of 30 per cent[7] and 28 per cent[8] of patients not operated on after esophageal bleeding.

Although we fully recognize the possibility that the two groups of cases are not entirely comparable, it is of interest to compare the survival figures of Ratnoff and Patek[7] in 106 cases of cirrhosis after the first episode of bleeding with the survival figures in our group. Ratnoff and Patek reported a survival of only 30 per cent at the end of the first year and 20 per cent at the end of five years. Figure 2 super-

imposes the survival curve of the 36 cirrhotic patients in our group of 125 patients who have had shunt surgery after hemorrhage from esophageal varices and who have been followed for at least five years on the original curve of Ratnoff and Patek.[7] The decreased mortality is striking in the group operated on, showing a survival of 75 per cent of patients at the end of the first year compared with 30 per cent in those not operated on, and 57 per cent at the end of five years compared to 20 per cent in the group not operated on. Though the number of cases in this series of cirrhotic patients operated on after bleeding and surviving to be followed for at least five years is relatively small, we believe that the increased longevity of this group

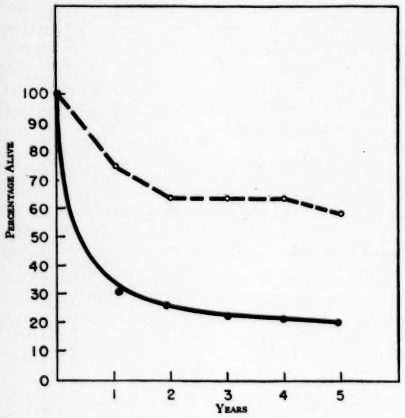

FIGURE 2. *Five-Year-Survival Curve of 36 Cirrhotic Patients after Shunt Surgery for Esophageal Bleeding, the Solid Line Representing the Series of Ratnoff and Patek[7] (Reproduced with the Permission of the Publishers) and the Broken Line Our Series in the Present Study.*

as compared to 30 per cent survival after five years in other reported series of medically treated cirrhotic patients is highly significant and encouraging.[7,9]

Frequency of Bleeding

Table 4 gives data regarding the occurrence of postoperative esophageal bleeding in the patients under study. From this it is apparent that 18, or 15 per cent, of these patients had some degree of bleeding postoperatively. There were only 2 deaths from esophageal bleeding postoperatively, representing a mortality of less than 2 per cent. This figure is much smaller than any expected mortality from esophageal bleeding in patients who have not had shunt surgery. The occurrence of bleeding after shunt operations on the patients with normal liver biopsies was 26 per cent compared to 12 per cent in the cirrhotic group. Bleeding was more frequent in the splenorenal group than in the portacaval, and greatest in patients who had makeshift shunts.

Status of Varices after Shunt Surgery

From the beginning it has seemed to us that if one could successfully reduce portal hypertension by per-

TABLE 4. *Summary of Postshunt Esophageal Bleeding.*

Group	Type of Shunt	Patients Operated on	Patients with Bleeding	Patients Dead from Bleeding
Patients with normal livers (5)	Splenorenal	14	2(14.3%)	
	Portacaval	2	0	
	Makeshift	3	3(100.0%)	
Patients with cirrhosis (13)	Splenorenal	74	12(17.0%)	2
	Portacaval	30	1(3.0%)	
	Makeshift	2	0	
	Totals	125	18(14.9%)	2

forming a venous anastomosis between the portal and systemic circulations one should see a decrease in size or disappearance of esophageal varices. The results of the postoperative roentgenologic examination of the esophagus in 76 of these patients (Table 5) are most encouraging and correlate very well with the decreased occurrence of bleeding previously mentioned. There was a marked reduction in the size of varices in 81 per cent of the patients who had splenorenal shunts. After 37 per cent of these shunts no varices were demonstrated. Eighty-four per cent of

TABLE 5. *Status of Varices after Shunt Surgery.*

Status	Patients with Splenorenal Anastomoses	Patients with Portacaval Shunts	Patients with Makeshift Shunts	Totals
Total examined	54	19	3	76
No varices	20(37%)	9(47%)		29(39%)
Varices smaller	24(44%)	7(37%)		31(41%)
Varices unchanged	7	3	3	13
Varices larger	3			3

the portacaval shunts showed similar diminution in size of varices, and in 47 per cent of these shunts no varices were demonstrated. There was no evidence of reduction of the size of the varices in any of the makeshift shunts that we have been able to examine postoperatively.

Figure 3 shows dramatically the disappearance of varices after shunt surgery in 1 of these patients, and to our minds is irrefutable evidence that the portal pressure is markedly reduced in patients on whom successful shunts have been performed.

Figure 4 presents another patient with extensive varices before operation; the center x-ray film still shows the presence of varices two weeks after the shunt, and the film on the right shows the esophagus to be free of demonstrable varices in the same patient two years after operation. In the early days of our experience with this operation we were disappointed to find no x-ray evidence of diminution in the size of

FIGURE 3. *X-Ray Films of the Esophagus in a Patient with Portal Hypertension, Showing Large Varices before Splenorenal Anastomosis (Left) and Virtual Disappearance of Varices Sixteen Months after Operation (Right).*

the varices in the immediate postoperative period. We have subsequently learned, as Figure 4 demonstrates, that it takes some time for the varices to disappear or become smaller.

LIVER FUNCTION

We have personally examined 52 of those patients now living and reviewed reports from the remaining 30 or their present physicians, or both. As a result we have classified them into three groups. The first comprises 55 patients who are doing well, carrying on a full program of work or household duties, and without any important physical limitations of which they are aware. The second group comprises 21 patients who are reasonably active but with some definite limitation. Nine of these have limitations due to progressive cirrhosis, 7 are handicapped by recurring episodes of bleeding, and the remaining 5 have disease unrelated to their liver disease or portal hypertension. The third group comprises 6 patients, each of whom is incapacitated by cirrhosis of the liver. Out of 82 living patients only 15, or 18 per cent, have enough disturbance of liver function to cause them to be aware of some degree of incapacity.

We have obtained laboratory data on the liver function of as many of the living patients as possible (Table 6).

Serum Albumin

Of 62 determinations of the serum albumin level, 29 per cent are higher, 53 per cent are equal to, and 18 per cent are lower than the preoperative levels in the same patients. In determining these figures we have considered a change of 0.5 gm. per 100 ml. to be significant. Eleven patients have levels below 3 gm. per 100 ml. Nine of these were classified in Group 2 or 3 above, and only 2 of them are in Group 1 and doing well without limitations.

Serum Bilirubin

Determinations of total serum bilirubin were available for preoperative and follow-up comparison in 61 patients. Thirty per cent showed improvement, 50 per cent were the same, and 20 per cent had increased levels. A change of 0.5 mg. per 100 ml. in this determination has been considered significant. Twenty patients now have bilirubin levels of 1.5 mg. per 100 ml. or higher. There appears to be no important correlation with the results of this test and the clinical grouping mentioned above.

Cephalin Flocculation

Determinations of cephalin flocculation in 61 patients revealed 40 per cent showing improvement, 40 per cent remaining the same and 20 per cent being worse than before operation. An increase or decrease of + at forty-eight hours in this test was considered a significant change. There are only 2 patients with a cephalin flocculation of + + or less who are not doing well. Of 14 patients with a + + + + test, 12 have other evidence of poor liver function, and 2 are clinically doing well.

TABLE 6. *Liver Function after Shunt Surgery.*

STATUS	SERUM ALBUMIN*	CEPHALIN FLOCCULATION†	SERUM BILIRUBIN†	BROMSULFALEIN RETENTION‡
	%	%	%	%
Improved	29	40	30	23
Same	53	40	50	31
Worse	18	20	20	46

*62 patients.
†61 patients.
‡48 patients.

Bromsulfalein

Bromsulfalein determinations (5 mg. per kilogram of body weight) were performed in 48 patients; the test was not done in patients who were obviously jaundiced. A change of 5 per cent retention at forty-five minutes was considered significant. Twenty-three per cent of the patients showed improved results, 31 per cent no change, and 46 per cent increased impairment of this functional test. One can-

not rely solely on this test as a guide to determine the well-being of the patient.

Hemoglobin

It is of interest that the hemoglobin determination in 74 patients is 12 gm. per 100 ml. or higher in all but 10, and in only 3 is it below 11 gm. per 100 ml. Each of these 3 has continued to have recurrent gastrointestinal bleeding.

these patients after operation. Such improvement had not occurred before operation even in the face of prolonged adequate medical treatment. The changes include improved feeling of well-being and strength, improved general appearance with restoration of normal skin color, return of normal fullness of face and normal musculature with surprising weight gain, regrowth of previously sparse axillary and pubic hair, and in some cases disappearance of

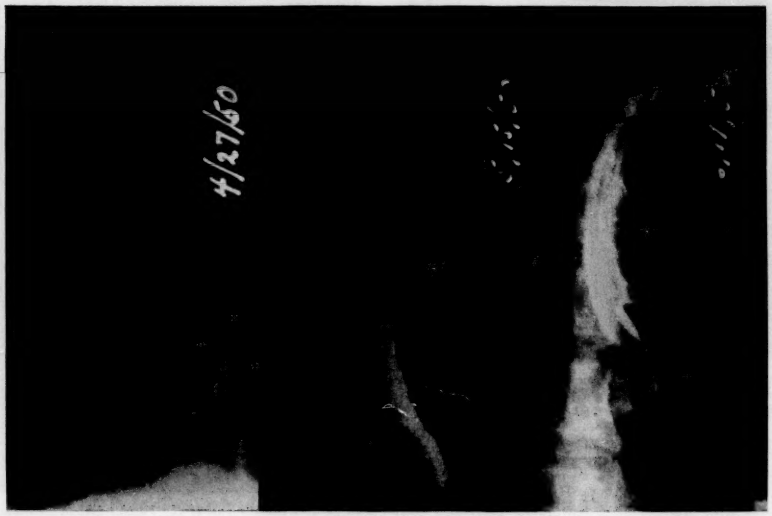

FIGURE 4. *Esophageal X-Ray Films in a Patient with Portal Hypertension before (Left), Two Weeks after (Center) and Two Years after (Right) Portacaval Shunt.*
Varices are still present two weeks after operation but have disappeared in the film taken two years after operation.

DISCUSSION

The lack of available standards for a similar group of patients not operated on makes evaluation of the laboratory data difficult. It seems clear that there is no proof in these data that venous-shunt surgery in itself leads to more impairment of liver function than would normally occur in patients with portal hypertension. This probably does not hold true in patients who have little liver dysfunction to begin with and in whom adequate collateral circulation has not developed before shunt surgery. An important number of the patients have improved liver function as shown by the results of the tests reported above.

So much for the evaluation of liver function as measured by these laboratory tests. One of the most striking things that we have noticed in addition to the decreased occurrence of bleeding has been the dramatic clinical improvement in a large number of ascites and edema. Figures 5 and 6 clearly demonstrate these changes in 1 patient. It is of interest that this clinical improvement is not necessarily accompanied by appreciable improvement in the liver-function tests.

There is experimental evidence that relief of portal pressure produced in dogs will lead to marked weight gain and general clinical improvement in these animals.[10] We believe that we are seeing the same sort of thing, perhaps to a more marked degree, in many patients whose portal hypertension is relieved by venous-shunt surgery. As Bollman has also suggested, it is quite possible that this procedure leads to improved physiology in organ systems such as the small intestine, as well as in the liver itself.

In conclusion, we believe this to be a most important group of cases and recognize that the patients will have to be followed closely for another five years

before many of our questions about them and about the value of this form of therapy will be conclusively answered. At present, however, we are convinced that shunt surgery can be performed in patients with serious liver disease at a reasonable risk, and that such surgery can relieve portal hypertension and markedly reduce the occurrence of bleeding from esophageal varices, thereby lengthening the survival of these patients and, in the majority, improving the state of health. The improvement of liver function as measured by the tests employed is apparent in many cases, but is seldom commensurate with accompanying clinical improvement. This is due to the fact that our tests are but crude measurements and, we suspect, to the fact that there is improved physiology elsewhere in addition to that in the liver itself.

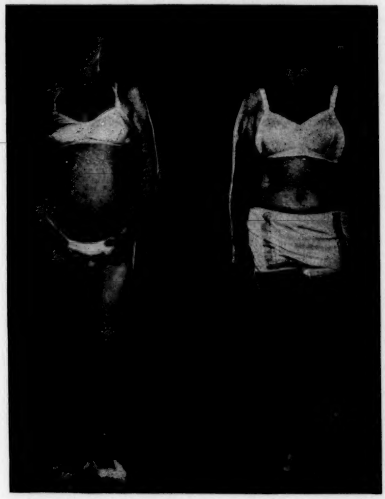

FIGURE 5. *Appearance of a Patient with Portal Hypertension before Operation after Two Years of Medical Treatment (Left) and Six Months after Splenectomy and Spenorenal Shunt (Right).*

SUMMARY

Follow-up studies on 125 patients who have had portacaval or splenorenal shunts for portal hypertension are reported. The length of the follow-up period was one to ten years.

The over-all mortality was 29 per cent. The operative mortality was 11 per cent.

By comparison with other reported series without operation the occurrence of bleeding was markedly reduced and life was prolonged.

Of 76 patients re-examined by roentgenologic study, 80 per cent have been shown to have reduction in the size of the esophageal varices. This we interpret as evidence of reduced portal pressure.

In addition, there may be demonstrable evidence of improvement in liver function clinically and by laboratory tests.

FIGURE 6. *Profile Views of the Patient Shown in Figure 5.*

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PITUITARY TUMORS

A Borderland between Cranial and Trans-sphenoidal Surgery

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THE purpose of this paper is to discuss the treatment of pituitary tumors, which lies in the borderland between cranial and trans-sphenoidal surgery.

FIRST PERIOD

Search for a Method of Reaching Pituitary Tumors

Historically, the search for methods that would best reach pituitary tumors began in the years 1904-1910. During this period cranial as well as trans-sphenoidal approaches were employed. The pioneering trials of this period were marked by high mortality.

SECOND PERIOD

Efforts to Reduce the Operative Risk

Cranial surgery. The next decade (1910-1920) found the surgeons striving for the improvement of both types of surgery to reduce the high operative risk. Cushing worked at lowering the mortality in cranial surgery; I take the responsibility for the trans-sphenoidal surgery. Cushing's review of his series of 105 patients operated on by the cranial method (1912-1932) shows a case mortality of 4.5 per cent in chromophobe adenomas and of 20 per cent in eosinophil adenomas.[1] Since his time the over-all case mortality in the chromophobe adenomas has been reported as 11.2 per cent by Grant.[2] None of the neurosurgeons present at the meeting of the American Medical Association at which he discussed this problem claimed better results.[3] The mortality in craniopharyngiomas is reported by various neurosurgeons[5] as 30 to 40 per cent. It should be mentioned that the fatality rate for chromophobe adenomas includes cases of large upward extension; Jefferson's[4] figure for small adenomas is much lower — 2 per cent.

Trans-sphenoidal surgery. The review of my own series of 413 patients, on whom I carried out trans-sphenoidal operations, showed an over-all mortality of 6 per cent,[5] including the pioneering trials. After antibiotics came into use, my cases showed a mortality of only 1.5 per cent.[6] Included in my series are craniopharyngiomas and tumors with cranial extension.

The low mortality of trans-sphenoidal surgery induced Cushing[7] and Frazier[8] to favor this method at a very early date.

Frazier's[9] series (1926) of operation by trans-sphenoidal surgery showed a mortality of 4.5 per cent in 53 patients, and Cushing's 1939 series a case mortality of 5.2 per cent in 227 patients.

In 1912 Cushing[7] wrote that the approach that he favored was, except for the sublabial incision, "to all intents and purposes similar to the endonasal method which Hirsch has recently described and which he has successfully practiced in a number of patients." Cushing used the trans-sphenoidal approach during his years in Boston, from 1912 to 1930. One of his biographers erroneously ascribed the trans-sphenoidal method to Cushing himself.[10]

THIRD PERIOD

Postoperative Radiation

A problem emerged of equal importance to that of reducing mortality. Although surgery did bring about improvement the effect was often not lasting. My explanation for this was that the tumor, which has caused visual disturbances, has long before burst the bounds of the sella and grown into the cranial cavity. Neither the cranial[11] nor the trans-sphenoidal technic can remove a tumor of this size in its entirety. To prevent regrowth of the remaining tumor, and even to achieve its shrinkage, I applied (not implanted) radium locally. By providing, at the end of the operation, a permanent access to the tumor remnants, I was able to make this radium application an office procedure.

A plaque, loaded with radium and shielded by heavy platinum on all sides except the radiating surface, is attached to a copper rod. After the nasal cavity is painted by cocaine and Neo-Synephrine, the plaque is placed in contact with the surface of the tumor remnant and fixed in position by a simple device. It required almost ten years, over the period of 1911-1921, to find, empirically, the effective dosage. Only by this combination of surgery and postoperative radium treatment was it finally possible to achieve lasting results.

FOURTH PERIOD

Publication of Lasting Results

Another ten years elapsed before it was possible for me to gather sufficient data on the duration of freedom from symptoms, especially the visual ones, after combined surgical and radium treatment. For the purpose of this report a patient was considered improved if his vision was restored to normal or if it became better, or if further deterioration of his vision was prevented. He was considered not improved if his vision continued to deteriorate after operation.

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In 1929 I was able to present the results in 161 patients treated by the combination of surgery and radium application since 1919, a period of ten years.[12]

In 1932 the number of patients who had undergone surgery had reached 175; the case mortality was 5.1 per cent. Of these patients 57 lived four and a half to thirteen and a half years after the operation; 41, or 74. 5 per cent, of these showed lasting improvement. These were the first reported series of cases with lasting improvement.[13]

In 1937 (at the end of the preantibiotic era) the number of patients who had been operated on for pituitary tumors and treated postoperatively by radium application was 277. The case mortality was 5.4 per cent. The follow-up period for the 262 survivors was nineteen years.

Of the 262 postoperative survivors 128 were operated on five to nineteen years before this review was made (in December, 1937), and they were alive at that time. Of these 128 patients 83 showed lasting improvement. In addition 12 were known to be improved during their lifetime, for a period of five to nineteen years after operation.

In summary, then, of 140 patients undergoing operations five to nineteen years before the date of the review, 95 (68 per cent) showed lasting improvement.

Long-lasting results. Concerning 25 patients who lived for nineteen and a half to thirty-four years after operation I succeeded in obtaining information despite the difficulties occasioned by World War II. Two of these patients had acromegaly. Twenty-three of them had chromophobe adenomas and were operated on because of visual disturbances; 21 of this group showed improvement lasting nineteen and a half to thirty-four years.

Fifth Period (Antibiotic Era, 1945-1955)

During the past ten years (the gap between 1937 and 1945 is due to World War II), recently by invitation of Dr. James C. White, I have operated with Dr. Hannibal Hamlin, of the Massachusetts General Hospital, on 67 patients, with 1 operative death (case mortality of 1.5 per cent). This series included 12 craniopharyngiomas.

Two of these 67 patients were women seventy-eight and seventy-five years of age with advanced visual disturbances caused by chromophobe adenoma. The seventy-five-year-old patient is now in her tenth postoperative year and is enjoying preserved, useful vision. The counterpart is a three-and-a-half-year-old girl almost blind at the time of operation as a result of craniopharyngioma. Today, six and a half years after operation, she has normal vision in one eye.

X-Ray Treatment

X-ray treatment of pituitary tumors was successfully begun in 1909,[14] during the same decade that saw the first surgical attempt made, and it has been continuously improved. As reported by various writers, x-ray therapy has been successful in from 26 to 43 per cent of patients with chromophobe tumors and from 40 to 63 per cent or even higher in eosinophil tumors.[15-17]

X-ray treatment of pituitary tumors is assumed to involve no risk, which is true in a general way. Both surgeons and roentgenologists have reported emergencies brought about as a result of this kind of therapy.[3,17]

Five years ago a rotational type of x-ray treatment, using a 2,000,000-volt machine, was introduced.[18] This form of therapy avoids epilation. So far 18.4 per cent of patients given high-voltage treatment have subsequently required surgery.[19] High voltage is now given preference, and the same author who a year previously classified pituitary lesions among the brain tumors suitable for surgery now recommends high-voltage treatment as a primary therapeutic measure.[20]

However, the operative risk of 1.5 per cent with the trans-sphenoidal method is so small, and the figure for lasting improvement (five to thirty-four years) so satisfactory, that I see no reason to prefer x-ray treatment, which has yet to be proved permanently effective. I should not entirely avoid this form of treatment of pituitary tumors: after all, in some otherwise unmanageable cases, it is a last resort. But until a longer follow-up period is possible, one cannot be sure of final results, and high-voltage therapy was introduced only five years ago.

One cannot disregard the recent warnings and advice of Arnold, Bailey and Harvey[21] that "it [is] inadvisable to give large doses of radiation to patients with slowly growing neoplasms within or near the brain stem . . . [and that] surgical decompression . . . should be done in these cases."

The trans-sphenoidal technic and postoperative radium application is in accordance with the recommendation of these authors in that the radium is applied directly to the tumor remnants *after* the operation.

Discussion

The results achieved by trans-sphenoidal surgery in the treatment of pituitary tumors deserve attention. The mortality with the intracranial approach, as universally reported, was almost twice as high as the rate with trans-sphenoidal surgery in the period before antibiotics were used. With the advent of antibiotics, the over-all mortality risk of cranial surgery, as recorded in the statistics of Grant,[2] Horrax et al.[19,20] and Davidoff and Feiring,[16] has been seven times that of trans-sphenoidal surgery. This statement includes operations on craniopharyngioma as well as the notoriously dangerous adenomas that have extended upward or laterally far beyond the region of the optic chiasm. This advantage of the trans-sphenoidal operation is reduced if the neurosurgeon avoids the transfrontal attack on the giant suprasellar extensions; in these cases the trans-sphenoidal approach also has little to offer (White and Cobb[22]).

In the favorable type of adenoma the trans-sphenoidal approach is safer because the site of these neoplasms is for the most part extradural. Only the uppermost segment of a pituitary tumor eventually becomes covered by the pia arachnoid. The mortality for trans-sphenoidal surgery was low even without the aid of antibiotics because this approach is primarily extradural.

The trans-sphenoidal method aims first of all at decompression of the chiasm. It reaches this goal by removal of the bony floor of the sella, excision of its dura periosteum, excochleation of the intrasellar portion of the tumor and, eventually, drainage of any broken-down cystic content. Since all these procedures are extradural, the mortality risk is naturally lower than that of the more radical transcranial approach beneath the frontal lobe.

Finally, the tumor remnants must be prevented from growing, and an attempt made to shrink them. This goal can be reached by local radium application or by x-ray treatment.

In spite of these obvious advantages of the trans-sphenoidal method, there is some prejudice against its use, based on a fear of infection and the criticism that the surgeon cannot clearly visualize the tumor. The antibiotics, however, have reduced infection to a minimum. The other criticism is based on inadequate knowledge of the technic involved in the use of the trans-sphenoidal approach.

The septum is, of course, a narrow plate. But after carrying out submucous resection of the septum, the surgeon spreads the mucoperiosteal flaps apart with a nasal speculum to the width of *both* nasal and *both* sphenoidal cavities. The operation is carried out in a newly created, wide tunnel that has no communication with the nasal cavities except for the first linear incision, thus preventing or restricting possible infection. The exposure of the sella is as a rule almost bloodless; each millimeter is visible in the reflected light.

The tumors amenable to this method are those causing visual disturbances. Cases of acromegaly are generally not suited to it when there are a small sella and no visual disturbances.

Summary and Conclusions

The best treatment for pituitary tumors is still open to discussion. Three methods are available: cranial surgery, trans-sphenoidal surgery, and irradiation by either radium or x-rays.

Trans-sphenoidal operations on 413 patients with pituitary tumors are analyzed.

Of 277 patients undergoing surgery in the pre-antibiotic era (1919-1937, inclusive), 262 survived, a mortality of 5.4 per cent. Of 65 patients (12 with craniopharyngioma and 3 with cranial extension) operated on in the antibiotic era, only 1 died — a mortality of 1.5 per cent.

A nineteen-year follow-up study revealed that 68 per cent of the patients showed improvement lasting for 5 to 19 years.

That life-long cure can be effected is proved by the finding that 23 patients retained and are retaining improvement over a period of nineteen and a half to thirty-four years.

Experience with the high-voltage x-ray machine, though promising, is as yet not sufficient to indicate whether results are lasting or whether there may be complications.

As a rule radiation should be used only if the character of the tumor has been established by biopsy.

Occasionally, all three methods of treatment are called for.

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TIMED-DISINTEGRATION CAPSULES

An in Vivo Roentgenographic Study

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BROOKLYN, NEW YORK

THE purpose of timed-disintegration capsules is to provide sustained therapeutic effect throughout the daytime period by administration of a single capsule in the morning. In this way the inconvenience and uncertainty attending administration of the drug three times daily are eliminated.

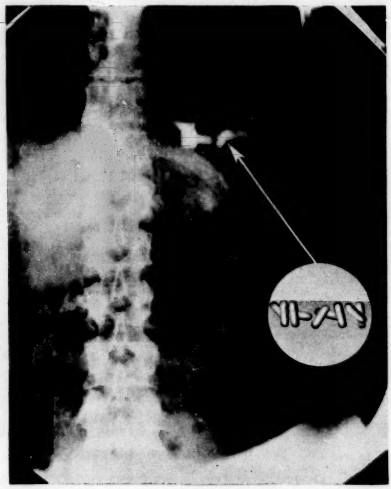

FIGURE 1. *Roentgenogram Taken Immediately after Ingestion.*
On the right the capsules are shown floating in the stomach contents below the water level. A glass of water was taken with the capsules.

Timed disintegration may be accomplished by incorporation inside the capsule of a number of tiny pellets variously coated for different disintegration intervals to cover the desired span of action.

LITERATURE

Very little has been published on the subject of timed-disintegration capsules. In describing the dosage of dextroamphetamine sulfate, *New and Nonofficial Remedies*,[1] 1955 states: "A capsule containing 10 or 15 mg. of dextro amphetamine incorporated into variably coated pellets which afford continuous release of the drug over a period of 8 to 10 hours, thus prolonging the therapeutic effect for 10 to 12 hours, may be administered once daily in the morning to adults in place of ordinary oral medication in divided amounts."

In the past, interest was focused on enteric capsules used for the purpose of bypassing the stomach. Cook and Martin,[2] in 1951, described the application of salol coating and glutoid capsules under the heading of enteric capsules and also discussed keratin, resin and shellac coatings. They stressed the uncertainties and cautioned that, if the capsules are too lightly coated, they dissolve in the stomach; on the other hand, if too heavily coated, they pass through the alimentary tract without dissolving.

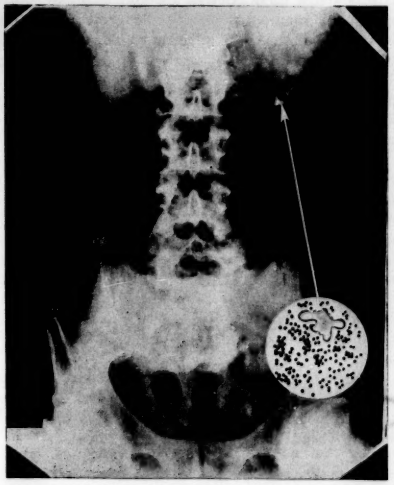

FIGURE 2. *Roentgenogram Taken after Two Hours.*
On the right dissolved granules are shown in a nebulous blob. Most of the granules are undissolved and dispersed. Approximately a third of the opaque medium is dispersed. A large mass lies over the sacrum in the ileum.

In 1935 Bukey and Rhodes[3] reported that an entire batch of one so-called enteric-coated tablet dissolved in the stomach, as shown by x-ray films, and that a second lot from a different manufacturer was 81 per cent efficient. A shellac coating was found to have no value for enteric medication, a salol-shellac mixture was 50 per cent, and a salol-resin mixture was 63 per cent efficient.

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†Roentgenographic technician, New York State.

Bukey and Bliven,[4] in 1936, reported that less than 10 per cent of the salol coatings that they had tried proved to be enteric. Since other workers have also condemned salol coating, the need for original research to determine the efficacy of all coating intended to delay the release of the active ingredient is apparent.

Confusion on this subject has been increased by widespread dissemination to the medical profession of an artist's conception of timed disintegration. This drawing gives the erroneous impression that the mass of capsule contents remains in a single blob. As shown by the data presented below, it is unsafe and unscientific to draw conclusions concerning timed disintegration on a theoretical basis.

The true disintegration timing and action of specially coated capsules or tablets can be determined accurately only by in vivo roentgenographic studies. Cook and Martin[5] have analyzed the problem as follows:

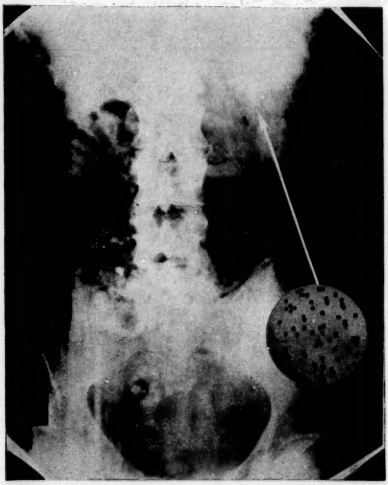

FIGURE 3. *Roentgenogram Taken after Four Hours. On the right all granules are small, discrete and undispersed. Scattering has occurred during the two-hour period between this and the previous roentgenogram.*

> In testing the efficiency of processes for rendering capsules or pills enteric, the use of a fluoroscope or an X-ray machine is necessary to determine what has happened. If the pill or capsule has been made from barium sulfate or bismuth subnitrate, it can readily be seen in the alimentary tract and its location determined if it has not disintegrated.

SCOPE OF INVESTIGATION

Contrary to the common impression, the roentgenographic studies reported below have shown that the contents of timed-disintegration capsules are scattered widely throughout the length of the gastrointestinal tract before the individual particles disperse or dissolve. The popular concept that the mass of the capsule contents remains in a single blob was gained from a composite drawing used for advertising purposes in widespread use.

The purpose of this report, therefore, is to analyze the results of actual roentgenographic studies that exactly delineate the mechanism of scattering, dispersion and absorption of the contents of timed-disintegration capsules.

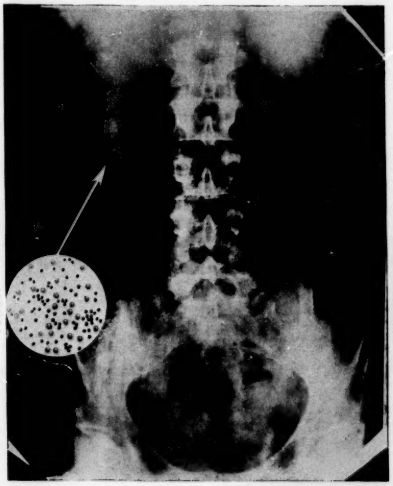

FIGURE 4. *Roentgenogram Taken after Six Hours. On the left the granules are spread out. A third of the granules show small water-logged blobs having a slightly nebulous appearance. The remainder of the granules are still discrete. The dispersing granules have moved out of the stomach and duodenum.*

PROCEDURE

The capsules* used in this study contained four different kinds of granules as follows:

Barium sulfate, *U.S.P.*: 5-mg. granules for immediate disintegration.

Barium sulfate, *U.S.P.*: 5-mg. granules for timed disintegration within approximately two hours.

Barium sulfate, *U.S.P.*: 5-mg. granules for timed disintegration within approximately four hours.

Barium sulfate, *U.S.P.*: 5-mg. granules for timed disintegration within approximately six hours.

In these capsules, the radiopaque barium sulfate was substituted for the usual active medication.

*Supplied by Nysco Laboratories, Incorporated, Long Island City, New York.

Subjects chosen for the investigation were average patients with no gastrointestinal disturbance and no contributory physical findings. Altogether 10 separate series were investigated; the illustrations are taken from 1 case typical of the average for the group.

The procedure adopted began at 8 a.m. Breakfast was withheld and 10 of the capsules were ingested with a glass of water.

A roentgenogram was taken immediately. Thereafter, examination was repeated at two, four, six, eight and ten hours.

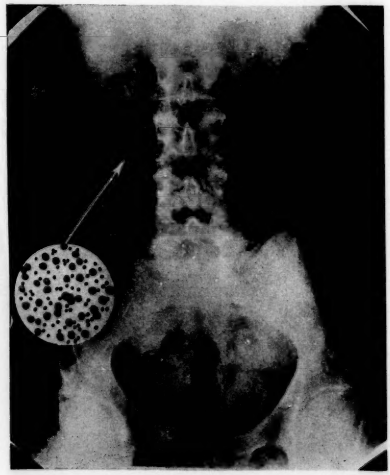

FIGURE 5. *Roentgenogram Taken after Eight Hours. The details on the left show the granules more spread out, with greater dispersion, and a small fraction of granules still unaffected.*

RESULTS

The roentgenograms in this series (Fig. 1-7) give graphic evidence of the process of dissolution, scattering and disintegration of these specially designed capsules and their contents.

The fact that the roentgenographic technic is an in vivo method is considered to indicate that it offers a more accurate picture than other procedures.[6]

As shown in Figure 1, taken immediately, the capsules float just below the liquid level in the stomach, owing to the entrapped air in the capsule. Since the entire capsule is immersed, however, the outside gelatin capsule dissolves as soon as it possibly can because it is completely surrounded by liquid. The contents (a third of the opaque medium substituted for the active ingredients), which are encased in the capsule without being incorporated in a timed-disintegration granule, will then be immediately available to the body.

As shown in Figure 2, taken after two hours, the gelatin capsule and the contents that immediately disintegrated remain in the stomach. The remainder of the contents are scattered throughout the stomach region, duodenum and part of the small intestine. A large mass lies over the sacrum in the ileum. Disintegration of some of the granules has just begun. This represents a longer disintegration time than that revealed by the in vitro modified *U.S.P.* technic.[5]

In Figure 3, taken after four hours, the granules are much more widely scattered throughout the length of the small intestine. The great bulk of granules has left the stomach. Some of the granules are beginning to disintegrate. This is revealed by the slightly swollen appearance. Free barium is in the lower ileum in large amounts, with traces in the ascending colon.

In Figure 4, taken after six hours, many of the granules have started to fill the ascending and transverse colon. Approximately a third of the granules show disintegration by swelling to small, radiolucent masses. This disintegration would make a soluble, active ingredient available to the body between four-hour and six-hour points. This is later than that revealed by the in vitro modified *U.S.P.* technic[5] for measurement of disintegration time.

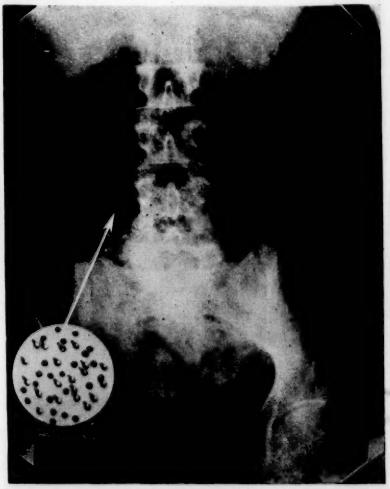

FIGURE 6. *Roentgenogram Taken after Ten Hours. The details on the left show all the granules to be water logged and more dispersed. At this point a soluble active ingredient would be completely dissolved. The blobs are more transparent and larger and show trails.*

In Figure 5, taken after eight hours, the water-logged granules are completely disintegrated globules. The remaining third of the granules are beginning to disintegrate. Barium has reached the splenic flexure.

In Figure 6, taken after ten hours, all granules are disintegrated. The remaining third of the granules have disintegrated between the eight-hour and ten-hour points. This is longer than the time indicated by the in vitro modified *U.S.P.* technic.[5]

In Figure 7, taken after twelve hours, all granules have become partly radiolucent and fully disintegrated. The swirling motion in the bowel is indicated by the trails noted after the blobs. Opacity is seen to reach the distal portion of the descending colon.

Table 1 summarizes the results.

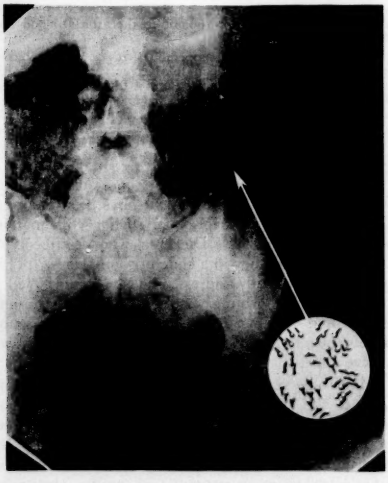

FIGURE 7. *Roentgenogram Taken after Twelve Hours. The details on the right show all the granules dispersed.*

CONCLUSIONS

The roentgenographic technic demonstrates a longer disintegration time than the modified *U.S.P.* disintegration-time technic.

Generally, whether the minimum or maximum time is required (that is, whether two or six hours are required when the disintegration occurs over a period of two to six hours) depends on the solubility of the active ingredient. The more soluble active ingredients would require minimum time, whereas the less soluble ingredients would tend to require the maximum time.

TABLE 1. *Comparative Disintegration Time.*

PORTION	MODIFIED *U. S. P.* TECHNIC[5]	ROENTGENOGRAPHIC TECHNIC
	DISINTEGRATION TIME	DISINTEGRATION TIME
1st part (5 mg.)	As soon as gelatin capsule disintegrates (5-10 min.)	Same
1st 1/3 of timed-disintegration portion (5 mg.)	2 hr.	2- 4 hr.
2d 1/3 of timed-disintegration portion (5 mg.)	4 hr.	4- 6 hr.
Remaining portion of timed-disintegration capsules (5 mg.)	6 hr.	6-10 hr.

It is believed that the roentgenographic technic offers a more accurate picture because it is an in vivo method.

The great convenience of the timed-disintegration capsule makes it an ideal method for the administration of drugs usually given in three divided doses.

150 Woodruff Avenue

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SPECIAL ARTICLE

THE CARE OF THE PATIENT*

C. SIDNEY BURWELL, M.D.†

BOSTON

IT is a great pleasure to have the privilege of representing the physicians of Boston in making these brief remarks at the opening of this distinguished meeting. Boston has good traditions of medicine and likes to think that the standards of thought and practice have been high since its early days. In the course of my remarks I propose to discuss certain general objectives of medicine and some general policies or principles by which these objectives may be realized.

This is a meeting of many doctors brought together by a common interest in medicine and in patients. It seems to me reasonable at the beginning of a meeting that is to discuss many technical aspects of medicine to attempt to set down some general principles.

Since it is a good rule to talk about the general problems of medicine in relation to a specific patient with specific problems, the text of my discourse is to be found in the following brief case history:

CASE REPORT

A 58-year-old man was admitted to the hospital with complaints of obesity, fatigue and somnolence. He reported that in the preceding months he had often found himself falling asleep while carrying on his daily work. Sometimes, he found it difficult to distinguish between reality and dreaming. He noted that his breathing was often rapid and shallow. He experienced several episodes of syncope. Ankle edema developed. These symptoms continued in spite of digitalis, diuretics and phlebotomy.

Physical examination showed an extremely obese man, who was 165 cm. (5 feet, 5 inches) tall and weighed 119.3 kg. (263 pounds). He was cyanotic and somnolent, and exhibited twitching movements of many muscle groups. His breathing was periodic, with alternating periods of apnea and tachypnea (but not hyperpnea). The chest movement appeared restricted, but the lungs were clear, and the heart normal in rhythm and sounds. The neck veins, however, were distended, and the liver extended 5 cm. below the rib margin. There was moderate edema of the ankles and an extraordinary degree of somnolence, so that this drowsy man often fell asleep in the middle of a sentence.

The laboratory work was instructive. The hematocrit was 65 per cent; the venous pressure was moderately elevated. X-ray films of the chest showed clear lung fields, an elevated diaphragm and an enlarged cardiac diameter. An electrocardiogram demonstrated atrial premature beats, low voltage and incomplete right-bundle-branch block.

The most illuminating laboratory work was that concerned with the measurement of pulmonary function. There was a normal diffusion in the lungs and a normal index of pulmonary mixing. The functional residual capacity was not abnormally high. The lung volumes and the ventilatory pattern, although abnormal, did not fit the diagnosis of emphysema or chronic pulmonary fibrosis.

The ventilatory response to increased concentrations of carbon dioxide in the inspired air was decreased at the time of admission. However, there was evidence that this was not on a central basis. The most significant abnormalities in this pattern of ventilation were reduction in the effective vital capacity, in the maximum breathing capacity and in the volume of alveolar ventilation per minute. The oxygen saturation of the arterial blood was only 84 per cent, and the pressure of carbon dioxide in the arterial blood was twice the normal value.

At this stage of study it appeared that the major physiologic dysfunction was inadequate alveolar ventilation, which had led to a low alveolar oxygen and a high alveolar carbon dioxide, both of which were reflected in the gas tensions in the arterial blood. Thus, this patient had chronic hypoxia and chronic hypercapnia, and these led in turn to cyanosis, polycythemia, somnolence, periodic breathing and the other symptoms, signs and disabilities.

Observations concerning one or more of the manifestations observed in this patient have been reported before. An early description of such a combination was written by Charles Dickens,[1] who described "A fat and red-faced boy in a state of somnolency." This boy was subsequently addressed by Mr. Samuel Weller successively as "Young Dropsy," "Young Opium-Eater" and "Young Boa Constrictor" — no doubt in reference to his obesity, his somnolence and his excessive appetite.

Many observers since Dickens have made contributions to the knowledge of this syndrome. Pertinent observations have been made in this laboratory on pulmonary function in obesity and in pregnancy by Merriman, Woodbury and Metcalfe,[2] and in various other laboratories on patients with ascites, obesity or pregnancy. In general, these observations have indicated that increasing abdominal girth is accompanied by a decreasing expiratory reserve and may lead to a state of relative ventilatory insufficiency.

In 1955 Sieker and his colleagues[3] at Duke University described 4 patients who exhibited extreme obesity, somnolence, periodic respirations, intermittent cyanosis, secondary polycythemia, right-axis deviation and decreased total lung volume, functional residual capacity and expiratory reserve volume. An important addition by these workers was the demonstration that many aspects of this syndrome were reversible by a sufficient loss of body weight.

It is known that obesity may itself alter the ventilation pattern and that it tends to cause shallow respiration. The working hypothesis in the case presented above was that the rapidly increasing weight of the previous year had led to mechanical conditions that

*Presented at the opening General Assembly of the Clinical Meeting of the American Medical Association, Boston, November 29, 1955.
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induced periods of shallow breathing, and that these periods set off in this patient the progressive and vicious circle leading to the pitiable state in which he presented himself.

The test of this hypothesis was what would happen to the pulmonary function and the patient's general status as his weight was reduced. He was placed on an 800-calorie diet, and no other treatment was carried out except phlebotomy. He lost approximately 18.1 kg. (40 pounds) in three weeks. The vital capacity rose from 1.6 to 3.6 liters, and the maximum breathing capacity from 42 to 122 liters. The arterial carbon dioxide fell from 75 to 45 mm., and the oxygen saturation rose from 84 per cent to normal. The actual volume of alveolar ventilation at rest more than doubled. At the end of this period of weight loss he was alert, responsive, no longer cyanotic and no longer twitching and, in general, his healthy and vigorous self.

In the weeks during which he was being studied there was opportunity to discuss with him the reasons for his recent gain in weight. He had always been heavy and always been a large eater because he liked food, but in the year before admission he had had a series of new anxieties and frustrations, and his increase in food intake had apparently been due to these emotional situations. As he said, "When I am in trouble I go to food as some people go to alcohol."

He is now active, reassured and confident, and still losing weight. He is considered to demonstrate a curable variety of heart and lung disorder responding promptly to appropriate treatment.

Objectives of Medical Practice

I now propose, with this patient in mind, to consider in the light of the history of medicine some of the objectives of the medical profession.

Medicine has an old and honorable history. Its distinguished past is in some danger of being forgotten in the excitement of the rapidly changing present. Medicine has changed with extraordinary rapidity in recent decades, and the medicine that I learned as a medical student forty years ago is in sharp contrast to the medicine of today. In many fields in this period clearer knowledge and understanding of the mechanisms of disease have tended to replace speculation and tradition. Physiologic processes have been unraveled. Pathogenesis is partly understood. Knowledge of the mechanisms of disease makes it possible in many happy cases to influence and to alter them toward the normal.

The problem of medical education has thus been altered. The assimilation of great numbers of facts is now not enough. It is necessary that the complex processes — physiologic, chemical, immunologic — that go on in the maintenance of health and the development of disease should be sufficiently understood so that informed action can assist the body in its adjustments to injury.

The growth of understanding has made it possible to improve the management of a variety of human situations. A few examples may be cited:

A number of infections have been brought under effective control partly by the deliberate modification of host reaction, and partly by specific measures against the invading organism.

The importance of homeostatic mechanisms has new appreciation — for example, doctors have learned to manipulate water and electrolytes and their distribution in the body so as to modify and mollify the sudden changes associated with disease, injury and operation.

Advancing knowledge of the physiology of the circulation has led to a more perceptive attack on the problems of circulatory disease than was possible in the absence of this understanding.

When an extract of thyroid gland was administered by Professor George Murray[4] in 1891, he began an era in which the hormonal control of bodily processes has been exploited to influence these processes favorably in the course of disease.

The patient described above is a specific example of this general principle. It was possible to find out what ailed him in terms of physiology and to take effective action.

These are examples (a longer list could be cited) of areas in which increased understanding has led to useful activity. This progress has been based on research, including the analysis of phenomena in living patients, the study of the morbid anatomy of patients who have died, experiments in living animals and the wide pursuit of chemistry, physics and mathematics in laboratories everywhere in the world. In a few minutes Dr. Shannon will discuss trends in medical research, and I do not mean to invade his territory. I do want to say that the present capacity of medicine to do good is better than it was because of research and because the research of the last fifty years has covered a wide spectrum involving *fundamental science,* human physiology and the study of the mechanisms of disease in patients.

The importance of understanding mechanisms underlying health and disease has set grave responsibilities for the investigator and equally grave responsibilities for medical education. The graduates of medical schools must be able to analyze the physiology of health and disease and thus to plan appropriate action. Medical education is now in a period of change calculated to meet a variety of needs. One of these needs is to maintain and deepen the undergraduate study of the basic sciences that underlie the modern science of medicine. Nothing, no matter how interesting, should be allowed to deprive the student of the indispensable discipline of the medical sciences.

However, to understand the phenomena of disease in terms of the science of medicine is not enough. There is also an *art* of medicine. This is defined as

the compassionate and helpful care of the patient as a person. Dana W. Atchley,[5] of New York, has made a brilliant analysis of this dual assignment of medicine: a clear statement of the importance of the science of medicine and an equally deep appreciation of the function of the physician as a healer. A few sentences from Dr. Atchley's article are worth quoting:

> It is thus apparent that the physician of today, at his best, represents a fusion of the healer and the scientist. In his role he analyzes the multiple components presented by a single human being. As healer his intuitive understanding of the personality and environment is amplified by modern psychology; and scientific studies of the many facets of the structure and function of the physical machine inform him as to the existing organic status. The appraisal resulting from an integration of these data leads naturally to the special management appropriate to the particular individual. The introduction of the highest possible standards of scientific precision into clinical medicine is no deterrent to the exhibition of compassion or any of the other generous gifts of the healer. Merging the healer and the scientist combines the best capacities of both and loses nothing by the union.

This leads one to ask if the emphasis on medical science and medical research has been accompanied by a loss of skill in something equally important in medicine — namely, the healing art. This question is not new. A classic and familiar article dealing with this problem is one by Francis W. Peabody (of Boston) entitled "The Care of the Patient," first published in 1927.[6] This lucid and beautiful expression of the successful combination of medical science and the art of healing has influenced the art and practice of doctors for nearly thirty years. I venture to let Dr. Peabody represent the medical tradition of Boston and read two paragraphs from his lecture:

> It is probably fortunate that most systems of education are constantly under the fire of general criticism, for if education were left solely in the hands of teachers the chances are good that it would soon deteriorate. Medical education, however, is less likely to suffer from such stagnation for whenever the lay public stops criticising the type of modern doctor the medical profession itself may be counted on to stir up the stagnant pool and cleanse it of its sedimentary deposit. The most common criticism made at present by older practitioners is that young graduates have been taught a great deal about the mechanism of disease but very little of the practice of medicine — or, to put it more bluntly, they are too "scientific" and do not know how to take care of patients.

Dr. Peabody concludes his charming discourse as follows:

> Disease in man is never exactly the same as disease in an experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. Thus the physician who attempts to take care of a patient, while he neglects this factor, is as unscientific as the investigator who neglects to control all the conditions that may affect his experiment. The good physician knows his patient through and through and his knowledge is bought dearly. Time, sympathy, and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret for the care of the patient is in caring for the patient.

From time to time one hears the opinion expressed that there is something about scientific medicine that is somehow incompatible with the compassionate and understanding care of a patient as an individual. One need not waste much time on this question. In a group highly trained in scientific medicine, as in any other group of persons, there will be varying degrees of aptitude and skill in the art of healing, but to say that scientific medicine and the art of healing are incompatible is historically just not so. The best answer is to look at individuals; everyone can think of individuals who are at once examples of the scientific physician and masters of the healing art.

These two methods, then, — the science of medicine and the healing art, — are the equipment of the doctor. Now, what is his job? A hundred years ago Laënnec said, "The object of medicine is the cure of disease." This is hardly adequate today, when all physicians are concerned not only with the cure of disease but also with the *prevention* of disease, the *maintenance* and *improvement* of health, the *rehabilitation* of injured or diseased persons, the modification of pathologic processes for the improvement of health, and the helping of patients to understand themselves and their problems of health so that they can manage their lives more effectively.

In meeting these enormous responsibilities, the medical practitioner has help from many sources. He has the continuing growth of medical knowledge (which implies a grave responsibility on him to keep up with it). He has the improving organization of medicine, which it is hoped will make expertness available without loss of the clear placement of responsibility on some one person to see the whole problem, to set the course and to steer the ship.

The physician has also assistance from the accumulated experience and skill of the human organism. This is so important that I propose to spend a few minutes discussing it. One of the hazards of having at hand many therapeutic devices for altering the course of disease is that if one is not careful one may lose touch with some of the built-in mechanisms that tend to heal or modify disease. Who, today, has much opportunity to observe the course of disease as dealt with by the machinery of the body and therefore to know what his own job as a physician may be? Dr. Jacob Bigelow (of Boston) wrote in 1835 a classic article entitled "Self-limited Diseases."[7] The concept of self-limitation of disease is worth exploring, especially in an age when enthusiasm about new knowledge may lead physicians to take credit that is not their due but belongs in part to the beautiful and on the whole successful mechanisms of the body itself. The survival of the race is a demonstration of the over-all success of these built-in methods, and practitioners of medicine will do well to pay attention to them, to use them and not to interfere with them. Dr. Bigelow writes as follows:

. . . we may suspect those complaints to be self-limited, in which it is observed that the unwary, and the sceptical, who neglect to resort to remedies, recover their health without them. We may also suspect diseases to be of this character, when we find opposite modes of treatment recommended, and their success vouched for, by practitioners of authority and veracity. . . .

. . . in many places, at the present day, a charm is popularly attached to what is called an active, bold, or heroic practice; and a corresponding reproach awaits the opposite course, which is cautious, palliative, and expectant. . . .

. . . The longer and the more philosophically we contemplate this subject, the more obvious it will appear, that the physician is but the minister and servant of nature; that in cases like those which have been engaging our consideration, we can do little more than follow in the train of disease, and endeavor to aid nature in her salutary intentions, or to remove obstacles out of her path. . . .

Conclusions

Physicians are, I hope, agreed on these principles of medical practice: to use the science of medicine; to use the art of medicine; and to exploit the inborn and ready-made skill of the experienced human organism.

These general objectives of medicine were met in the patient described above. The science of medicine made it possible to define and to relieve his disability. The art of medicine made it possible to bring to him understanding of his problems and to help him find the capacity to meet them. Some millions of years of evolution and adaptation enabled him to make an effective adjustment when thus aided by science and by art.

How fortunate one is to live in this age of medicine! Continuing changes and growth are expected and hoped for. Details will alter; I suspect that the principles of caring for the patient will remain.

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MEDICAL PROGRESS

CARCINOMA OF THE BREAST (Concluded)*

The Study and Treatment of the Patient

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BOSTON

VII–Planning Treatment for the Individual Patient

With facts gained from the observations and principles described in the foregoing brief account, we may now proceed to look at the patient in a broader frame of reference and to plan her treatment. Our current view of this all-important subject is briefly outlined in this section. In considering each patient, we seek to place her appropriately in the clinical setting ("type") and then answer the six questions posed at the outset of the section entitled "The Study of the Patient." These are, to recapitulate:

Where is the patient in the natural course of the disease?

What has local surgery to offer?

Is the tumor hormone stimulated?

If so, where are such hormones coming from?

Can administration of hormones or surgical withdrawal help?

Has irradiation a place?

In the ensuing account, 8 clinical types of the disease are distinguished for discussion. Any such distinction is obviously artificial since there is overlap and merging of the clinical appearances; these 8 groups of patients emerge as typifying the most salient problems.

Clinical Type A: the Early Case without Known Metastases in Young or Menopausal Women ("the Young and Early")

Stage of progression? Such patients are, by definition, early in their disease. Until further experience with the patient has been gained one has no way of knowing whether one is dealing with a disease of three months' or ten years' duration. This must depend on further observation and follow-up study.

Local surgery? Excisional biopsy must be done in virtually all cases. Simple mastectomy may be advisable as a biopsy procedure. Radical mastectomy should then be carried out. The standard radical

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operation described by Halsted or the modification described by Greenough may be used. The operation is aimed at removing the skin overlying the tumor, the breast containing the tumor and the entire lymphatic drainage of the pectoral and axillary regions.

Hormone stimulation? One can only fall back on the statistical fact that in women before senility, the vast majority of tumors show some degree of estrogen stimulation.

Source of hormones? One may safely assume that in young or menopausal women (and this includes by definition *women up to ten years after the menopause*) estrogen production by the ovary is playing a part. Therefore, determination of estrogen excretion in such patients and (if they are near or after the menopausal age group) of FSH is a useful preliminary to the next step.

Withdrawal or administration of hormones? In young women or in patients at or after the menopause who show significant estrogens in the urine (or a low FSH value), surgical castration should be done. There is no evidence that prophylactic administration of any hormone such as androgens, estrogens or cortisone has anything whatsoever to offer the patient at this stage.[1]

After castration, the patient should have a repeat check of the urinary estrogens and FSH values. This should show a low To value for estrogen and a high FSH. This lays the groundwork for subsequent study of adrenal estrogen production.

Irradiation? In such patients, irradiation has a role only if the axillary contents on pathological examination show tumor to be present. It should be emphasized that 15 to 30 per cent of axillas, judged clinically to be free of disease, will show metastases pathologically.[73,83] This is not a contraindication to radical mastectomy since it is the extensively involved and "loaded" axilla that is dangerous surgically. The presence of one or two small and even microscopic areas of metastatic disease changes one's treatment only in that it is a positive indication for postoperative irradiation.

Where the Stage 1 lesion is in the medial half of the breast, or where axillary lymph nodes are unexpectedly involved on microscopical examination, prophylactic irradiation of the internal mammary area is indicated. Routine biopsy of this chain through the second interspace appears surgically attractive. Pathologically, it is irrational since one has only a small likelihood of finding in that precise area the lymph node that will indicate or contraindicate lymphatic involvement; even if involved, the wisdom of surgical extension into the chest is questionable, as previously mentioned.

Clinical Type B: the Early Lesion without Known Spread, in the Senile Patient ("the Old and Early")

The measures described above for the young woman are applicable to the truly senile patient, largely depending on her systemic condition. If she is in good general health, we advise radical mastectomy. Study of urinary estrogens and FSH should, in all such cases, demonstrate low or absent estrogens by the To technic and a high FSH. If either of these is demonstrated otherwise, one may safely assume that some ovarian function is still present and that stromal hyperplasia may exist, and in this case castration should be carried out. If the patient is clinically and endocrinologically senile, with atrophic vaginitis, some facial hair growth and thin skin (and low urinary estrogens) one need not carry out castration. One should always be suspicious of the presence of cortical stromal hyperplasia; some surprisingly good results are obtained from castration in older women.

In some elderly women, particularly those with chronic cardiac, renal, hepatic or pulmonary disease with the cancer confined to the breast, there is a real place for simple mastectomy. The tumor may be very slowly growing, and such a procedure may tax the patient very little.

In elderly patients with advanced disease of other types and extremely slowly growing tumors in the breast, it may be wisest to leave the process entirely alone.

The following case illustrates avoidance of interference in the senile age group.

E.W. (P.B.B.H. 3J104), an 86-year-old woman, was admitted to the Peter Bent Brigham Hospital in December, 1955, suffering from cardiac failure. A history was obtained of a mass in the right breast of many years' duration. This mass, a characteristic scirrhous carcinoma 3 by 2 cm., lay lateral to the nipple. It was attached to the skin but not the pectoral fascia. No axillary lymph nodes were palpable.

She had not nursed her only child. The date of the menopause was difficult to establish, but it had occurred at about 50 years of age.

No treatment was advised and after the cardiac failure had been controlled, she was discharged. This decision was reached on the grounds that the optimum method of treatment, estrogen therapy, was contraindicated in the presence of cardiac failure. If left untreated, this slowly growing asymptomatic carcinoma had a prognosis of many years. The cardiac status was far more limiting to survival.

Clinical Type C: Limited Local Disease, with Slow Spread to the Soft Tissues, in Young or Menopausal Women ("Slow, No Bones")

Stage of progression? The fact that the spread to the axilla has been, according to the history, "slow" indicates that it is possible to orient the timing of spread. That the disease has spread slowly into the axilla suggests that it will continue to progress slowly. This is a form of disease that reacts favorably to extensive endocrine therapy.

Local surgery? Many of these patients first appear for treatment having had a mastectomy in the past. Further local surgery is inadvisable; local chest-wall recurrence may be a problem when the patient is first seen and is surely a hazard if a loaded axilla is invaded.

If mastectomy has not been done, in the presence of local and extensive axillary involvement (even

though the disease in the breast is limited), radical mastectomy is contraindicated. It is our conviction that some slowly progressing tumors have been converted into overwhelming systemic disease by operation at this stage.

There are certain cases in which, though the axilla appears negative or very favorable, local changes in the breast itself also contraindicate the radical operation. These changes include widespread areas of "peau d'orange," satellite skin nodules, direct extension of the tumor to the surrounding thoracic skin, fixation of the tumor to the chest wall and extension to the other breast.

The question of biopsy is often difficult in this group. As mentioned previously, it should be excisional, or by needle.

Hormone stimulation? Although experience has been small, there is a place here for the stilbestrol stimulation test. With no evidence of remote metastases, the chances of serious harm to the patient are negligible. On three days' dose of stilbestrol, the tumor may show increased local turgor and even redness. Such a test is valuable in determining the next step and laying the groundwork for further treatment.

Source of hormones? As in Group A above, study of estrogen and FSH excretion should be undertaken.

Withdrawal or administration of hormones? As in Group A above, castration is indicated in younger or menopausal women with evidence of estrogen activity. A positive stilbestrol stimulation test is an indication for castration. If the patient's Stage 2 lesion has already been treated by castration and local x-rays (described below), it is appropriate now to begin an initial course of inhibitory therapy with cortisone.

Irradiation? It is in this group that local irradiation of the tumor itself finds its greatest usefulness. A careful program of irradiation to the breast and axilla should be undertaken. This should include the supraclavicular area and the internal mammary chain. Slow, fractionated administration of x-rays may be of much greater value than intensive short-duration treatment. This is of vital importance when skin breakdown is imminent. In such cases, very gentle x-ray therapy, carried out over a long period,[84] may result in rescue rather than destruction of the overlying skin.

Clinical Type D: Rapid Spread of Local Disease with Minimal or No Skeletal Spread ("Fulminating")

Stage of progression? The inflammatory carcinoma falls under this heading. Taylor and Meltzer[85] describe two main clinical types: the primary type, in which the inflammatory signs and the mass appear simultaneously; and a secondary type, in which they are first seen in a breast already the seat of cancer. The latter occurs especially in women with large, pendulous breasts, and they present a wide variety of clinical types ranging from an amorphous appearance to that in which the spread is nodular, each nodule being surrounded by redness and edema.

The incidence of this form of disease is spread throughout the age groups in a manner similar to other types of mammary neoplasms except that it is rarely seen in the senile woman. In a series of 74 cases of inflammatory carcinoma reported from the Mayo Clinic,[86] only 1 was found to occur during lactation. When such a case does occur during pregnancy or lactation, the rapid advance of the tumor suggests that stimulation by pituitary hormones may be more important than stimulation by estrogens. Estrogenic levels are very high during pregnancy but fall to very low levels during lactation. This type of lesion, with a great deal of local disease and occasionally presenting carcinoma *en cuirasse* or spread through the ribs into the chest, is most unpromising. The disease when seen may be considered to be very far progressed in its course even though the duration in weeks is short.

Local surgery? Surgery to the breast has nothing to offer in this lesion.

Hormone stimulation? This question is difficult to answer in individual cases, and it is impossible to make any statistical prediction. In such patients, the use of the stilbestrol stimulation test appears to be extremely hazardous. If the patient is given cortisone with benefit, one may conclude that inhibition of adrenal production of estrogens has been effective.

Source of hormones? Surgical castration should be done in all such cases unless the patient is so near death that survival from the operation seems unlikely.

Hormone withdrawal or administration? After castration, an intensive course of therapy with cortisone is indicated. If the results of this and of x-ray therapy to the local lesion give the appearance of arrest of the disease, — a rare occurrence but one that has been seen, — one may consider a further step such as adrenalectomy or hypophysectomy. In our experience such procedures have been of little benefit in this situation.

Irradiation? Irradiation to the local disease and to the sites of presumed lymphatic spread constitutes the most effective form of treatment in this type of disease.

The following case illustrates a fulminating lesion in a young woman; the onset of *lactation with the disease* (apart from childbearing) points up a pituitary factor as clearly as endocrine study might. Pituitary surgery could not halt the progress.

B.P. (P.B.B.H. 5J242), a 34-year-old woman, underwent a radical mastectomy for carcinoma of the left breast in February, 1955. Axillary involvement was present, and she underwent x-ray sterilization; in May, a surgical castration was performed. At laparotomy, several small nodules were noted on the liver surface. In June, 1955, a small lump was seen in the mastectomy scar, and during the next month this grew with great rapidity.

Until x-ray sterilization, her periods had been regular. She had 3 children; the first was breast fed. The youngest child was 15 months of age.

On admission to the Peter Bent Brigham Hospital on July 10, 1955, she was found to have a mass covering the

left side of the chest deep to the mastectomy scar, which was raised, tense and purple. The right breast showed *peau d'orange*, and milk could be expressed from the nipple. There were clinically malignant lymph nodes in the right axilla. The liver was palpable.

Investigations revealed the presence of tumor cells in a smear of peripheral blood. The serum calcium was 6.0 milliequiv. per liter. FSH was positive in dilutions of 1:100. There was x-ray evidence of a mediastinal mass and pleural effusions.

In the hospital, the tumor grew at an alarming rate, and it was considered unjustifiable to carry out either estrogen stimulation or cortisone inhibition tests. Since time was urgent, a hypophysectomy was carried out without delay.

On July 27, hypophysectomy was performed, the patient obtained no relief and steadily failed, dying on the 14th day. Post-mortem examination revealed extensive local disease and involvement of the lungs, liver, pericardium, peritoneal cavity and bone marrow.

Clinical Type E: Late-Stage Disease with Involvement of Lungs, Liver or Brain or All Three ("Late, Visceral")

Stage of progression? The fact that lungs, liver or brain or all three are involved suggests that there is not much time left for the patient. These are the principal channels to death.

Local surgery? Radical mastectomy offers nothing. In certain cases simple mastectomy may have some palliative value. There may be cases in which local histologic identification of tissue is essential to establishment of the nature of remote metastases, particularly in the skull, liver or lungs.

Hormone stimulation? Here, again, one must rely wholly on statistics. In young women or women near or shortly after the menopause, one may assume that the tumor is probably endocrine stimulated. The use of stilbestrol stimulation is not justified because of the hazard to the patient. Watching for favorable results from cortisone inhibition is possibly justified, but end points are scarce unless clear-cut parenchymatous lesions in the lungs can be observed on x-ray study.

Source of hormones? In the younger and menopausal age groups, the ovaries may be considered to be the source of estrogen. Surgical castration is indicated. The presence of hepatic, pulmonary and cerebral metastases may occasionally contraindicate such a procedure, because of systemic illness. In this case, it may be more merciful to leave the patient alone, or to carry out x-ray castration. In such cases, unless they are clearly terminal, determination of urinary estrogen and FSH levels may provide a helpful guide to the usefulness of castration or other endocrine measures.

Withdrawal or administration of hormones? In conjunction with either surgical or x-ray castration, such patients should be started on a course of cortisone. They are late in the course of their disease, and there is not time to wait for long intervals between the sequences of treatment. If the tumor is hormone stimulated, the administration of cortisone may be helpful. However, with liver disease and cerebral disease, one must guard against possible deleterious effects. Adrenalectomy and hypophysectomy have been disappointing in these cases. The "snowball" lung lesion is more responsive to endocrine measures than the lymphangitic pulmonary spread; it is also more favorable than liver and brain involvement. In this group, as in those with the inflammatory disease, the use of estrogenic hormones either as test substances or for therapy is dangerous.

Irradiation? Irradiation castration is mentioned above. Where metastases in the thorax or abdomen produce profuse collections of fluid, one may achieve considerable palliation by the intraserous injection of radioactive gold.[87] In our experience, this has been more rewarding in the treatment of hydrothorax than in the treatment of ascites. It is important to remember that patients with carcinoma of the breast metastatic to the peritoneal cavity may have fluid in the chest without having actual cellular involvement of the lung or pleura. This, therefore, should be settled by thoracentesis and appropriate cell study before gold is instilled.

Irradiation of the lungs, liver or brain is usually unrewarding and should be undertaken only under exceptional circumstances.

The following case illustrates a fine result from oöphorectomy, with progress to a "hormone-independent" phase. With extensive visceral disease, as in this case, adrenalectomy fails.

S.P. (P.B.B.H. 5J339), a 48-year-old spinster, in 1945 underwent a radical mastectomy for carcinoma of the left breast. She had been aware of a mass in this breast for 7 years.

In 1950 metastases were demonstrated in the pelvic bones, ribs and lungs. A total hysterectomy, with bilateral oöphorectomy, was carried out; the osteolytic lesions underwent sclerosis; the pulmonary metastases disappeared, and the bone pain was relieved. This remission was maintained until February, 1954, when further osteolytic lesions were noted and treated with testosterone propionate and x-ray therapy. Complete relief was obtained.

In February, 1955, a further exacerbation occurred. This was treated with further testosterone therapy and cortisone, 50 mg. a day. No symptomatic or objective improvement was obtained.

The patient was admitted to the Peter Bent Brigham Hospital in September. She was in considerable pain. Physical examination revealed a wasted woman with no evidence of recurrence in the left radical mastectomy scar, with palpable left supraclavicular lymph nodes (proved positive on biopsy) and a liver felt 4 fingerbreadths below the right costal margin. On September 8 she underwent bilateral adrenalectomy. She obtained no symptomatic relief of bone pain; the hepatomegaly increased, and she steadily failed, dying 2 months postoperatively.

Clinical Type F: Slow Progression of the Disease with Skeletal Metastases ("Slow, with Bones")

Stage of progression? It is in these patients that it is most useful to orient the time progress of the disease. A patient who has had cancer of the breast and who now presents extensive skeletal metastases, no visceral involvement, little weight loss, good general health, tissue turgor, preservation of subcutaneous fat and normal blood and chemical values may have many years of useful life ahead. Carefully staged endocrine study and therapy are indicated.

This type of tumor appears to be virtually the most promising for palliation by endocrine therapy. It is not unusual to find patients with extensive skeletal

disease who have literally no evidence of soft-tissue involvement.

Local surgery? One may see these patients after initial surgery. If a radical mastectomy has previously been carried out, or if the local lesion is either very small or very large, with axillary metastases, local surgery is not necessary. Histologic confirmation of the lesion should not be attempted unless it can be done easily, without hazard of further spread. Excisional biopsy is preferable to incision of local masses for histologic confirmation.

If the local lesion is clearly delimited and freely movable and ulceration is threatened, simple mastectomy may be advisable despite widespread skeletal metastases. Irradiation locally should follow such surgery. Radical mastectomy is contraindicated.

Hormone stimulation? It is in this group that the study of calcium excretion achieves its usefulness. Patient should be placed on limited calcium diet, with urine collections shortly after admission to the hospital. It has been our practice to stop all endocrine therapy at the outset.

As mentioned previously, the stilbestrol stimulation test is contraindicated in the presence of hypercalcemia (levels of over 5.8 milliequiv. per liter), hypercalcinuria (values of over 300 mg. a day) or impaired renal function. In addition, a subtle factor of "systemic illness" enters into this equation. If the patient seems to be suffering a systemic illness from the disease, it is definitely unwise to use the stilbestrol stimulation test.

Lacking any of these contraindications, the stilbestrol stimulation test is the simplest and most direct way of approaching hormone therapy. Appropriate increase in serum calcium, urine calcium, pain or other systemic manifestations constitutes a positive test; the tumor is sensitive to hormone stimulation.

If the stilbestrol stimulation test is contraindicated, a cortisone inhibition test may be done, the same end points being used.

Source of hormones? If the patient is young or in the menopausal group, ovarian estrogens may be assumed to be active. Checking this by urinary estrogen and FSH determination is important to accurate therapy.

In patients as late as their middle seventies we have seen clinical benefit from castration. In some of these patients, stromal hyperplasia of the ovaries is found. The burden of proof should be placed on the surgeon who advises against castration as the first step in these cases.

After castration, one is in a position to assess the function of the adrenal glands. It should be emphasized that if x-ray castration has been done, precise estrogen and FSH studies should be undertaken, and if there is any suggestion of continued ovarian function, surgical castration should be carried out.

Hormone withdrawal or administration? If, after castration, the Tzn estrogens are elevated in the urine, or if there is continued evidence of growth stimulation of the tumor by the appearance of new osseous metastases, or a persistence of a high urine or serum calcium, adrenalectomy must be considered.

We are unable at present to offer clear-cut indications for the decision between adrenalectomy and hypophysectomy. It has been our practice to carry out adrenalectomy in patients who appear to have "a long way to go" and to reserve hypophysectomy for patients who appear to be nearer the end of their disease; this policy is being modified toward earlier hypophysectomy. The uncertain nature of indications at this stage should be emphasized in this review. We have seen several patients who fall into our most favorable results from hypophysectomy and who still have their adrenal glands in place. We have seen a rare patient seemingly made worse by adrenalectomy in whom hypophysectomy might have been a better first step. Only one thing is certain: all groups actively studying this problem are approaching hypophysectomy earlier in the disease as their experience grows. Previous adrenalectomy complicates the management of the postoperative hypophysectomy patient to a degree that may rob her of much palliation.

Irradiation? Here, as mentioned previously, local irradiation of symptomatic areas finds great usefulness.

The following case, which illustrates the usefulness of endocrine and chemical assay, emphasizes the hazards of stilbestrol and lateness of the menopause in a patient with cortical stromal hyperplasia:

M.S. (P.B.B.H. 3H261), a 73-year-old woman, had had a carcinoma excised from the left breast in a physician's office 2 months before admission.

She complained of pain in the ribs. She had had a natural menopause at the age of 53. Her only child had not been breast fed.

On examination her endocrine age was considered to be less than her true age. She had a recurrent tumor at the operative site.

Urine estrogen levels showed To, 1750 I.U., and Tzn, 3320 I.U., corroborating the clinical impression of estrogen activity. A stilbestrol stimulation test produced nausea, marked bone pain, mental confusion and stupor, and her condition deteriorated so rapidly that an "emergency ovariectomy" was carried out.

She made a rapid recovery and was discharged asymptomatic from the hospital 10 days later.

Postoperatively, urine estrogen levels showed a fall to 100 I.U. of To and 100 I.U. of Tzn, and urine calcium levels had fallen from the preoperative level of 120 to 60 mg. per 24 hours.

Microscopical study showed the ovaries to be the seat of cortical stromal hyperplasia. Improvement has been maintained.

Clinical Type G: in Pregnancy

The placenta, as an endocrine organ, is the source of large amounts of estrogens, which increase in titer throughout pregnancy. The objectives of treatment of cancer of the breast in this setting may be summarized under two headings: the local lesion is managed according to the same dictates that would otherwise govern; and the placenta and ovaries are removed as soon as possible. Matters of social, religious, emotional and familial import enter the equation and often are determining in the decision; certainly, in the third trimester, one can carry out

local treatment and await the advent of a viable fetus without too much danger unless the local tumor is "inflammatory."

Clinical Type H: Male Breast

Most of the comments about the progress of the disease in the younger menopausal age group in women apply to men. The prognosis of carcinoma of the male breast is generally worse than that in the female, as previously mentioned.

Indications for local surgery, local or remote x-ray therapy and endocrine medication and surgery are basically similar to those previously mentioned in the female, including the study of hormone stimulation and inhibition and calcium metabolism.

As a general rule, orchiectomy has an even more favorable effect on these patients than castration in the female. Favorable results from orchiectomy in these patients have been reported as high as 70 per cent,[63] somewhat higher than the favorable results of castration in the female.

VIII–Summary and Conclusions

A carefully planned approach to the patient with carcinoma of the breast involves study of the histologic, clinical and biologic types of the tumor, the state of its progression and its reaction to various hormones.

Accurate surgery, accurate endocrinology and accurate radiology are equally essential in achieving the curative or palliative results made available to the patient by recent advances in clinical science.

In this review the endocrine and metabolic study of the disease has been described, together with a status report on hormone therapy and the surgical operations of mastectomy, castration, adrenalectomy and hypophysectomy.

It should be mentioned in closing that as yet no patient with metastatic or reactivated cancer of the breast has been cured. Though it is cure that we seek — and frequently attain in the early lesion — it should not dominate our clinical planning. There is much to be offered in care even though cure is unattainable.

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MEDICAL INTELLIGENCE

EFFECT OF PENICILLINASE ON CIRCULATING PENICILLIN

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With the long-acting depot penicillins in general use today, prolonged blood levels also prolong the sensitivity reactions when they occur. The use of ACTH and cortisone as anti-inflammatory agents to overcome the reaction is helpful, but the penicillin is still circulating in the blood stream.

Penicillinase, an enzyme that hydrolyzes and inactivates penicillin, is formed by various bacteria (staphylococci, *Escherichia coli* and *Bacillus cereus*) and has previously only been used in bacteriologic mediums in vitro to inhibit penicillin in body fluids to be cultured. Its use in the treatment of penicillin reactions has not previously been suggested, studied or reported.

This study describes the action of penicillinase† on circulating penicillin in vivo in guinea pigs and human subjects. It was found that penicillinase in vivo consistently obliterated all circulating penicillin in both guinea pigs and human patients.

Experimental Studies

In paired groups of guinea pigs, 2 receiving only penicillin intraperitoneally and 2 receiving penicillin intraperitoneally combined with subcutaneously, it was found consistently that after a single injection of as little as 40,000 to 200,000 units of penicillinase, no circulating penicillin could be detected within an hour and over a period of seventy-six hours by the Kolmer broth-dilution method,[1] although injections of 500,000 to 800,000 units of penicillin were given every twenty-four to forty-eight hours for a total dosage of almost 2,000,000 units (Fig. 1). The inactivating action of penicillinase in vivo was found to be the same against both aqueous crystalline penicillin and procaine penicillin.

Before its in vivo action was studied in human subjects, the relatively crude and unsterile enzyme was purified by ammonium sulfate fractionation followed by dialysis to rid it of salts, followed by sterile filtration. This was done by Dr. Henry Lardy and Miss Shu Wang, of the Enzyme Institute, University of

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†Kindly supplied as Penicillinase-A by Dr. Bruno Puetzer, research director, Schenley Laboratories, Incorporated, New York City. It is obtained from cultures of *B. cereus*, strain NRRL-B569. The enzyme is precipitated by acetone, ethanol, dioxane, sodium tungstate and other protein precipitants.

Wisconsin. They determined the penicillinase activity of the threefold to fourfold fractionation purification by a polarimetric method,[2] using a Rudolph polarimeter and two decimeter tubes.

Toxicity studies were carried out in guinea pigs, which received 100,000 units of the crude enzyme daily intraperitoneally for two months. They remained well. Gross and microscopical study of sections of all vital organs, after death, revealed no changes.

Studies in Human Subjects

Twenty human beings (without penicillin reactions) were given daily injections of 800,000 units of fortified procaine penicillin twice a day intramuscularly. After consistent blood levels were established for several days, a single injection of 100,000 to 800,000 units of the purified penicillinase was given intramuscularly to each patient. Within an hour and for periods of four to seven days later, no circulating penicillin could be detected despite the fact that the injections of penicillin were continued twice a day (Fig. 2). In patients in whom the penicillin was

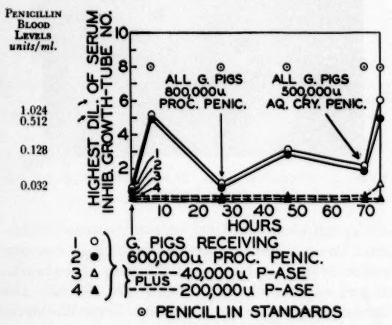

Figure 1. *Penicillin Blood Levels in Guinea Pigs after Penicillinase (P-ase).*

stopped when the penicillinase was injected, no circulating penicillin could afterwards be detected.

Discussion

The remarkable affinity of the enzyme for its substrate has been demonstrated in vivo in guinea pigs and human beings. Its prolonged action after a single injection was surprising. Apparently, its breakdown or excretion is not as rapid as that of penicillin. The enzyme penicillinase catalyzes the hydrolysis of the lactam ring of penicillin to produce penicilloic acid.[2,3] Penicilloic acid is devoid of any antibacterial activity and presumably is nonantigenic. Intradermal skin testing in a penicillin-sensitive person with aqueous crystalline penicillin produced a ++++ erythematous wheal reaction. In the same person, when the penicillin was mixed with penicillinase before injection, there was no reaction.

The absence of toxicity after a single injection of purified penicillinase in guinea pigs and human subjects has also been shown. Repeated injections of penicillinase in guinea pigs produced no toxic, hypersensitivity or anaphylactic reactions. Two patients were given three intramuscular injections each of 800,000 units of purified penicillinase eight days apart. No localized or generalized sensitivity reactions to the penicillinase were noted.

A follow-up study of the use of purified penicillinase in patients with penicillin reactions is under way and

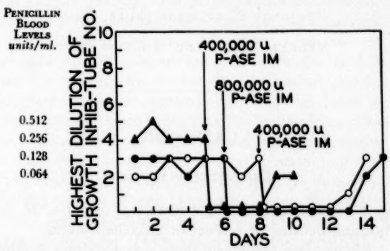

Figure 2. *Penicillin Blood Levels of 3 Patients Receiving 800,000 Units of Procaine Penicillin (Fortified with Aqueous Solution) Twice a Day Intramuscularly and Given a Single Dose of Penicillinase (P-ase) Intramuscularly.*

will be reported elsewhere. It is not expected that penicillinase will be completely effective against the vascular inflammatory reaction by itself, but rather that maximum benefit will result to the patient from its combined use with antihistamines or cortical steroid or ACTH or both. It is expected that, once all available antigen (penicillin) in the circulating blood stream and interstitial fluids is quickly hydrolyzed, the anti-inflammatory action of cortical steroids or ACTH will be more effective more quickly and the reaction less apt to recur.

Summary

Parenteral injection of penicillinase in guinea pigs and human subjects given penicillin resulted in rapid disappearance of detectable circulating penicillin. After a single injection of penicillinase no circulating penicillin was detected for several days, even though injections of penicillin were continued twice a day. No local or systemic toxic manifestations from purified penicillinase were noted in the guinea pigs or human subjects studied.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42201

PRESENTATION OF CASE

A forty-seven-year-old woman was admitted to the hospital because of a fever of unknown origin.

Eleven days previously there was a sudden shaking chill with a fever. After several days of bed rest the fever gradually subsided. Six days before admission the fever recurred and persisted, the temperature rising to as high as 103°F. Despite the administration of acetyl salicylic acid, the temperature remained elevated.

Two and a half years previously an active duodenal ulcer was demonstrated by x-ray examination, and the patient was placed on an ulcer regimen. Eight months before entry a splenorenal venous shunt with splenectomy was performed because of intractable ascites resulting from cirrhosis of the liver. At operation the pelvic organs, intestines and stomach appeared normal. An upper gastrointestinal series showed large esophageal and gastric varices and scarring of the duodenum, without evidence of an active ulcer. An intravenous pyelogram was normal. After the operation the patient became free of ascites. Three months before admission she noted the onset of hot flashes, and the menstrual periods ceased except for occasional staining.

Physical examination showed a well nourished woman without jaundice or lymphadenopathy. The lungs were normal. The heart was not enlarged. A Grade 2 systolic murmur that was loudest in the pulmonic area was audible along the left sternal border. Examination of the abdomen was negative except for a healed operative incision. Pelvic and rectal examination revealed a smooth, firm cervix; a hard, nontender, slightly movable mass that filled the pelvis was believed to consist of uterus on the right side and a mass extending to the left in the region of the ovary.

The temperature was 103.2°F., the pulse 84, and the respirations 24. The blood pressure was 125 systolic, 65 diastolic.

The urine gave a + test for albumin; the sediment of a catheterized specimen contained 3 red cells and an occasional white cell per high-power field; culture grew out moderate coliform bacilli. The urinary urobilinogen was 1.5 Ehrlich units. The Aschheim–Zondek test was negative. Examination of the blood revealed a hemoglobin of 11.9 gm. per 100 ml. and a white-cell count of 19,000, with 67 per cent neutrophils. The nonprotein nitrogen was 22 mg., the total protein 64 gm., the albumin 3.8 gm., the globulin 2.6 gm., and the bilirubin 1.8 mg. per 100 ml. The alkaline phosphatase was 10.7 units. Cephalin flocculation was + + in forty-eight hours. The prothrombin content was 100 per cent. Numerous blood cultures, the blood Hinton test and Widal and brucella agglutination tests were negative. A stool specimen gave a negative guaiac test; culture was negative for enteric pathogens. An x-ray film of the chest was normal. An abdominal film demonstrated a small calcification overlying the right wing of the ilium and mild degenerative changes about both hips. A soft-tissue mass was present within the bony pelvis (Fig. 1).

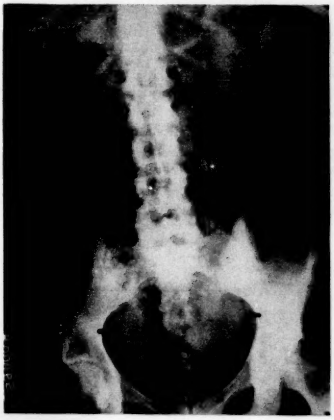

FIGURE 1. *Abdominal Film, Showing Pelvic Soft-Tissue Mass (Arrows).*

Achromycin therapy failed to lower the temperature, which ranged between 99 and 104.2°F. The white-cell count ranged between 19,600 and 26,400. The pulse remained at about 80. On the thirteenth hospital day there was a shaking chill, and the temperature rose to 105.2°F. Examination of the abdomen showed tenderness, with spasm in the left lower quadrant, where there was a palpable mass. On the next day a sound was passed into the uterine fundus, which lay anteriorly and to the right of the

mid-line. A barium-enema examination demonstrated displacement of the proximal portion of the rectum and the rectosigmoid slightly to the right, and elevation of the sigmoid colon by the pelvic mass on the left (Fig. 2).

FIGURE 2. *Right Anterior Oblique View of the Barium-Filled Colon, Showing Upward Displacement of the Sigmoid (Arrows) and Straightening of the Rectum by the Mass.*

On the eighteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. HOWARD ULFELDER*: For the purpose of discussion, I shall concentrate on the pelvic mass. First, I should like to characterize it as accurately as possible from the information available. Eight months before admission at the time of an abdominal operation no mass was felt in this area; on admission it was palpable on pelvic and rectal examination and about two weeks later, on abdominal operation. There is every indication, therefore, that the mass was not present eight months before admission, but had developed since then and actually increased in size during the two weeks of hospitalization. When the patient was first admitted to the hospital the mass was hard. Hard may mean a great many things: it may mean fluid under great tension or a solid mass, whose consistence may vary from rubbery to stony hard. Although I do not know exactly what is meant by the word "hard," I choose to interpret it as meaning a solid, rather than a cystic mass. At the time of admission the mass was described as nontender on pelvic and rectal examination. Later, tenderness developed in the left lower quadrant, where the mass was. As I interpret the description in the protocol, this was a single mass, perhaps rounded or symmetrical but definitely not a cluster of masses or a grossly nodular mass. There is reasonable evidence that the mass was fixed. If this were a simple ovarian cyst that was not adherent to the adjacent peritoneum, it would float upward out of the pelvis and leave the uterus in its normal central position. The marked displacement to the right of the uterus means that the mass could not move and was fixed in the peritoneum or was retroperitoneal. Can you help me, Dr. Wilson?

DR. RICHARD V. WILSON: As the protocol stated, the rectum and the rectosigmoid junction are displaced to the right, and the sigmoid is elevated by the mass (Fig. 1 and 2). The most helpful point is the fact that films taken both two years and eight months before admission also show the mass. One can see a shadow in the earliest film that is similar to but smaller than that in the later films. Unfortunately, the present film is overexposed, but the mass is roughly the same size here as on the film eight months previously. We never visualized the left ureter in the vicinity of the mass. There is no dilatation of the upper portion of the ureter on the left side, however. The right ureter is seen in relation to the mass eight months before admission and is not displaced.

DR. ULFELDER: Is the bladder shadow shown?

DR. WILSON: The bladder is not compressed. We did not try to distend the bladder because the mass was not mentioned at the time. The x-ray film was taken to determine whether the patient had a satisfactory dye excretion by the left kidney. I did the barium-enema examination at the time that she was complaining of a minor degree of tenderness of the sigmoid; there was slight spasm in the sigmoid colon adjacent to the mass, but no intrinsic change within the colon itself.

DR. ULFELDER: On the basis of what Dr. Wilson has said, I must correct my previous statements to the extent that the patient did have the mass eight months previously. Perhaps the fact that it was demonstrable in the x-ray films at that time but not easily palpable at operation is significant. To me it is evidence in favor of a retroperitoneal site of origin. It would be easy to slip a hand into the pelvis through an upper abdominal incision and interpret a mass felt posterior to the pouch of Douglas as sacrum or some other normal retroperitoneal structure rather than an extraneous mass. I do not think a mass of this size within the peritoneal cavity would escape even casual palpation so I shall assume that the mass was of much longer standing than I had realized from reading the protocol and that the evidence points more strongly toward a retroperitoneal rather than an intraperitoneal site of origin.

Was the kidney removed at the time of the splenorenal shunt?

DR. ROBERT E. SCULLY: No.

DR. ULFELDER: Was an intravenous pyelogram taken during the present illness?

*Chief, Gynecological Service, Massachusetts General Hospital.

DR. WILSON: No; the patient was sensitive to the dye at the time of the first examination eight months before admission.

DR. ULFELDER: To summarize the character of this mass, it was of long standing, increased in size slightly but definitely over an interval of eight months, was almost certainly larger two weeks after admission, apparently was solid rather than cystic, was smooth and nontender on admission, but perhaps became tender later on. What could this mass have been? It could have been a left tubo-ovarian abscess, which would explain many of the findings including the fixation, the onset of fever and chills and the gradual increase in size. Nothing in the history gives us an additional clue that this might be salpingitis or salpingo-oöphoritis, but such a clue is not necessary. This could have been an ovarian cyst, which had become inflamed and adherent locally and perhaps had become secondarily infected. Most ovarian cysts do not contain pus, but occasionally secondary infection develops within one and can produce this picture. Cancer of the ovary, although less likely, is another possibility. The consistence of the mass is not that of solid ovarian cancer, but certainly could be that of cystic ovarian cancer.

The mass is not likely to have been a large fibroid of the uterus because of its continued increase in size while the patient was going through a reasonably normal menopause; a fibroid during the menopause should decrease in size.

Lymphoma should be mentioned. The clinical picture on admission was consistent with this diagnosis. The location of the mass and its behavior under observation certainly are characteristic of a retroperitoneal lymphomatous mass in this area.

Diverticulitis might also be mentioned. However, the evidence of the barium-enema examination is against it. The patient not only had no diverticula, but, more important, no signs of irritated adjacent bowel, which would be present in a diverticulitis producing a mass of this size in the pelvis.

A remote possibility is perforated duodenal ulcer. It has been mentioned that she had a duodenal ulcer in the past; this may have perforated, sealed off and localized in the pelvis on the left side. However, many features of the mass noted in the x-ray examination are not consistent with that type of collection; therefore, I shall exclude this possibility.

A liver abscess, pylephlebitis, with which the clinical picture on admission was entirely consistent, was certainly not indicated by any other of the findings. The patient was not quite sick enough for that. The pulse never rose significantly, and the illness was characterized primarily by chills and fever, with remissions and with leukocytosis.

I wish that a pyelogram had been taken on admission, because I should like to believe that the clinical features that this patient presented were the result of obstruction of the left ureter by the mass, with a superimposed urinary-tract infection, manifesting itself by fever, chills and a positive culture of the urine for *Escherichia coli*. I could then assume that the mass failed to become tender because it was not in itself the cause of the fever of unknown origin, but was the cause of it indirectly by pressure on the left ureter. However, very few cells were noted in the sediment of the catheterized specimen, and there was no tenderness of the left kidney, so I shall discard this explanation.

I have not gone into a detailed discussion of the laboratory findings, for it seems to me that most of them are consistent with the known chronic liver disease and not necessarily associated with the mass. I assume that bizarre causes of fever such as malaria have been excluded.

In conclusion, I believe that this patient had a mass in the left side of the pelvis and that it was probably tubo-ovarian in origin. It was equivalent to a retroperitoneal mass because of adherence to the adjacent peritoneum. I shall assume that the source of the fever was the mass itself. My final diagnosis is a tubo-ovarian abscess.

DR. SCULLY: Dr. Francis M. Ingersoll followed the patient's course preoperatively. Two or three weeks before the operation, when he first saw her, he believed that the mass in the region of the left adnexa might be an ovarian cyst. Several days preoperatively, he elicited tenderness in the left lower quadrant. He then believed that an inflammatory lesion must be present in the pelvis and wondered whether it was a pyometrium. After a uterine sound was passed and no material was obtained, he concluded that the most probable diagnosis was tubo-ovarian abscess.

CLINICAL DIAGNOSIS

Tubo-ovarian abscess, left.

DR. HOWARD ULFELDER'S DIAGNOSIS

Tubo-ovarian abscess, left.

ANATOMICAL DIAGNOSIS

Tubo-ovarian abscess, left.

PATHOLOGICAL DISCUSSION

DR. SCULLY: I shall read from the operative note: "The sigmoid and the uterus were densely adherent to an inflammatory mass in the region of the left ovary. By blunt and sharp dissection the sigmoid was freed from the mass which was entered and found to be infected." The inflammatory mass, which involved the left tube and ovary, was removed; after this a hysterectomy and right-sided salpingo-oöphorectomy were done. Pathologically, the left tube was dilated, contained purulent exudate and was densely adherent to the ovary, which was greatly enlarged, measuring 10 cm. in diameter. It was ragged in several places where the capsules of abscesses had been ruptured.

The right tube and ovary were densely adherent, but there was no abscess formation on this side. Microscopically, the inflammatory process appeared subacute, and I think it was perfectly consistent with a duration of a month or so. Whether or not it could have been present much before that time is difficult to say.

DR. WILSON: The shadow was first seen in the x-ray films eight months before admission.

DR. SCULLY: I suppose it is possible that an acute salpingo-oöphoritis was superimposed on an older process, or that ovarian cysts had been present eight months before admission and subsequently became infected.

CASE 42202

PRESENTATION OF CASE

First admission. A seventy-five-year-old man entered the hospital because of pain in the back.

Three weeks previously he noted constant severe pain in the lower portion of the back and the right hip and thigh that became worse and caused him to be bed ridden. A vague pain in the shoulders and posterior portion of the neck also appeared. Other symptoms were several nosebleeds, a cough productive of whitish sputum and progressive anorexia. A few weeks before admission a stone was passed in the urine, and there were several episodes of hematuria.

Fifteen years before admission, because of hematuria, a cystogram was taken, and a large diverticulum in the left posterior portion of the urinary bladder was demonstrated. Two years before entry a prostatectomy was performed at another hospital because of urinary obstruction. A small carcinoma of the urinary bladder was found and treated by implantation of radioactive gold needles. He then remained well until the onset of the present illness.

Physical examination showed a pale, dehydrated, fatigued man. Examination of the chest revealed rales at the left-lung base. The heart was not enlarged. A Grade 1, apical, systolic murmur was audible. The abdomen was soft and nontender, with normal peristaltic sounds and no palpable masses. Slight tenderness was noted in the right flank. There was a healed suprapubic scar. Punch tenderness was present over the fourth and fifth lumbar and first sacral vertebras. The raising of the legs to a straight position caused pain in the lower part of the back bilaterally. Rectal examination showed good sphincter tone. The prostate felt soft. One observer felt a soft-tissue mass beneath the pubis to the left of the prostate.

The temperature was 98°F., the pulse 112, and the respirations 20. The blood pressure was 140 systolic, 95 diastolic.

The urine gave a +++ test for albumin; the sediment contained 40 red cells and numerous white cells per high-power field; a culture grew out *Proteus vulgaris*. Examination of the blood revealed a hemoglobin of 10.5 gm. per 100 ml. and a white-cell count of 7600. The nonprotein nitrogen was 20 mg. per 100 ml. The sodium, potassium and chloride were normal. The alkaline phosphatase was 19 units, and the acid phosphatase 2.9 units, with no prostatic acid phosphatase. A stool specimen gave a negative guaiac test. X-ray films of the chest demonstrated some linear densities at the right-lung base and some prominence of the heart in the region of the left ventricle. Films of the lumbar spine and pelvis showed severe degenerative arthritic changes involving the lumbar spine, with narrowing of all the intervertebral-disk spaces and large spurs along the margins of the bodies; degenerative arthritic changes of both hips with enlargement of the femoral heads, narrowing of joint spaces and proliferative changes; and both acetabula shallower than usual, particularly on the right side. Three metal clips were seen in the right side of the true pelvis opposite the ischial spine. Intravenous pyelograms demonstrated prompt excretion of the dye from both kidneys in good concentration; the kidneys and ureters appeared normal; three radon seeds were noted in the right aspect of the urinary bladder, where there was a poorly defined filling defect. A barium-enema examination showed diverticula of the sigmoid and questionable pathologic narrowing of the rectosigmoid junction.

Cystoscopic examination was negative, except for some obstructing tissue in the vesical neck; culture of the bladder urine grew out abundant coliform bacilli. The patient was comfortable with salicylate therapy and bed boards. There were no urinary symptoms. He was discharged on the thirteenth hospital day.

Final admission (one month later). In the interval the patient felt well and was able to ambulate daily in spite of persistent discomfort caused by pain in the back and hips. Except for moderate frequency there were no urinary symptoms. He was readmitted to the hospital for urethral dilatation.

Physical examination showed no significant changes.

The urine gave a + test for albumin; the sediment contained a rare red cell, 2 white cells and +++ bacteria per high-power field. Examination of the blood revealed a hemoglobin of 5.9 gm. per 100 ml., with 1.6 per cent reticulocytes, and a white-cell count of 10,300, with 1 per cent late myelocytes, 6 per cent metamyelocytes, 12 per cent band forms, 59 per cent neutrophils, 12 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils. A smear showed slight achromia and polychromasia and a slight decrease in platelets. The nonprotein nitrogen was 14 mg. and the bilirubin 0.3 mg. per 100 ml. The sodium, potassium, chloride and carbon dioxide were normal. The alkaline phosphatase was 23.6 units. The prothrombin content was 83 per cent. The Coombs test was negative. Two stool specimens gave negative guaiac tests.

The urethra was dilated, and the patient placed on constant bladder drainage with an indwelling catheter.

He gradually became weaker and unresponsive and died on the thirty-first hospital day. The hemoglobin fell to 4.7 gm. per 100 ml. terminally.

Differential Diagnosis

Dr. William D. Sohier*: This last paragraph is a masterpiece: it covers approximately a month of hospitalization and tells nothing helpful.

Before the first admission the patient had a pain in the back that progressed in severity so that within three weeks he was bed ridden. That, together with nosebleeds, cough, anorexia and the stone that was passed in the urine, makes one immediately consider a malignant process involving lung and bones, with a reduction in platelets and severe hypercalcuria. On the other hand the urinary infection and obstruction together could well have accounted for the stone. The tenderness to punch over the fourth and fifth lumbar and first sacral vertebras noted on admission supports the diagnosis of metastatic disease of the bone. I do not believe I have ever seen a patient, even with severe degenerative joint disease of the spine, who exhibited tenderness to punch — that is, pain on direct pressure. May we see the x-ray films?

Dr. Richard V. Wilson: On the barium-enema examination the spleen appears large. On many of the films it cannot be seen because of the tremendous amount of air in the intestines. Multiple diverticula were mentioned, but there is no evidence of diverticulitis. In the lung there is a shadow in the right-lung base for which I have no explanation. It may be the result of an infectious process or of atelectasis secondary to a small tumor. A tiny density on the right, somewhat high for a nipple shadow, may be a small nodule in the lung. In the urinary bladder there is a vague difference in the density of the dye that could be the result of a small recurrence. However, one can see the outer border of the bladder. I cannot exclude a small recurrence, but I am not sure that one is present. I do not find any evidence of tumor in the bones. There is generalized osteoporosis and marked degenerative changes, with narrowing of nearly all the interspaces of the joints. The interspaces of both hip joints are markedly narrowed. There are large spurs, but I do not see any bone destruction.

Dr. Sohier: Is the osteoporosis of the severity that one would expect for the patient's age?

Dr. Wilson: Yes.

Dr. Sohier: Do you see any Paget's disease?

Dr. Wilson: No.

Dr. Sohier: Pathologic narrowing of the rectosigmoid junction was mentioned in the protocol.

Dr. Wilson: It was not seen fluoroscopically.

Dr. Sohier: Among the important points in the protocol is the elevation of the alkaline phosphatase on two occasions. This must be considered in the differential diagnosis, unless one assumes that there was a small amount of Paget's disease hidden in the skull, or that there were liver metastases manifested only by elevated alkaline phosphatase. There were no skull films. The most important finding, however, is in the examination of the blood. There was a moderate anemia and a white-cell count of 7600 on the first admission. Was a differential done?

Dr. Bernard M. Jacobson: There were 70 per cent neutrophils, 11 per cent lymphocytes, 10 per cent monocytes and 4 per cent metamyelocytes, 4 per cent band forms and 1 per cent basophils.

Dr. Sohier: On both the first and last admissions there was no suggestion of blood loss in the stool, but over a period of a month the hemoglobin dropped by half. The second hemoglobin value was 5.9 gm. per 100 ml., and the red cells on the smear showed slight polychromasia. The fact that the reticulocyte count was 1.6 per cent is important in that it suggests that there was some inflammation or irritation of the bone marrow. If this had been a toxic depression, I should expect much less than 1.6 per cent reticulocytes. It is too bad that mention was not made of one or two normoblasts. On the last admission was the patient running a fever?

Dr. Jacobson: The temperature, most of the time, was below 100°F. by rectum; terminally, it rose to 101°F. or so.

Dr. Sohier: Was a calcium or phosphorus determination done on the serum?

Dr. Jacobson: No.

Dr. Sohier: Was therapy given for the urinary-tract infection — Chloromycetin, for example?

Dr. Jacobson: No.

Dr. Sohier: In the differential diagnosis I must take into account the progressive anemia, with evidence of regeneration or perhaps irritation in the peripheral blood, and the elevation of the alkaline phosphatase. I shall consider two main possibilities; the first is infection. For some time the patient had a urinary-tract infection. However, there were no ragged edges on the intravenous pyelogram, and there was no evidence of nitrogen retention. I do not think that I can ascribe the progressive anemia to renal infection alone, without the presence of azotemia. Subacute bacterial endocarditis is a notable cause of severe anemia, particularly in older patients. Severe anemia may be the first and most obvious disability. I do not believe, however, that this patient had subacute bacterial endocarditis. Although there was a Grade 1 systolic murmur, no mention was made of whether or not it changed in character. In older persons uremia is also a common complication of endocarditis, and there was no evidence of uremia here.

Tuberculosis sometimes causes severe pancytopenia because of diffuse involvement of the bone marrow. However, as a rule in such cases the white-cell and platelet counts are depressed. That was not the case in the patient under discussion.

The second possibility is neoplasia. I think that

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this blood picture fits diffuse involvement of the bone marrow with neoplastic tissue very well. As I visualize it, patients with metastatic disease have metastases to active marrow in the ribs, spine and calvarium; as the anemia develops, there is a compensatory increase in the total amount of marrow because of the appearance of hematopoietic marrow in the fatty tissue of the long bones. With the increase in circulation to the areas of new marrow, the tumor cells are carried there. More recently another component of the anemia accompanying metastatic malignant processes has been discovered — that is, the latent hemolytic element. This has been proved by the shortened survival of the patient's own cells tagged with a radioactive chromate. Moreover, iron-turnover studies have shown that there is an increased disappearance of radioactive iron from the serum and an increased reappearance of radioactive iron in the red cells in patients with metastatic malignant processes. All these findings suggest that bone marrow, rather than being depressed in activity, is working perhaps normally or is more active than normal, but is unable to keep up with the moderate hemolytic element that is present.

What malignant process could have been invading the bone marrow? One that I am sure had been present is carcinoma of the bladder. There was some evidence on x-ray examination that there may have been a recurrence of this carcinoma. Carcinoma of the bladder usually metastasizes locally; it rarely metastasizes to the skin or bone. Geschickter and Copeland* mention 1 case of metastatic bladder carcinoma out of 334 cases of malignant neoplastic disease with metastases to bone. In the case under discussion we do not have any evidence of metastases to bone itself. I assume that the tumor was infiltrating through the marrow, although there may have been some bony involvement, causing the elevation of the alkaline phosphatase. I do not think carcinoma of the bladder, although it may have recurred locally, was the cause of the anemia or of death.

Carcinoma of the prostate commonly metastasizes to bone. The prostate was removed by the suprapubic approach. A small but anaplastic carcinoma may have been found on careful sectioning of the prostate. Metastases may have occurred two years before admission and may later have involved the bone marrow diffusely. Carcinoma of the prostate nearly always causes obvious changes on the x-ray film, and the metastases are osteoblastic in type. Geschickter and Copeland mentioned 1 case in which there was diffuse marrow metastasis without evidence of bony involvement in the x-ray films. In the case under discussion, although the serum acid phosphatase of 2.9 units was high normal, there was no elevation of prostatic acid phosphatase. Because there was no prostatic acid phosphatase and no evidence of osteoblastic lesions in the x-ray films of the bones, I shall set aside carcinoma of the prostate.

There was a suggestion of a lesion in the lung. Dr. Wilson demonstrated some atelectasis of the right lower lobe and a little nodule higher up in the right lung. Occasionally, a small, but anaplastic, carcinoma of the lung can occlude a bronchus and cause very little in the way of local symptoms but can metastasize widely to bone. I should like to see evidence of bony metastases on the x-ray film, but, again, this type of carcinoma can spread through the marrow without involving the bone directly. I think that this is quite a good possibility.

Carcinoma of the breast, thyroid gland, stomach and colon must also be considered. However, there is no evidence of their presence.

Multiple myeloma is a possibility. The patient was in the age group for multiple myeloma. The disease does diffusely invade bone marrow and frequently does not produce x-ray evidence of a lesion. Of course, one would like to see clear-cut holes in various bones or a washed-out appearance of the bones. Multiple myeloma, even when it involves bone widely, does not cause an elevation of the alkaline phosphatase because it is purely an osteolytic lesion. This makes myeloma less likely.

Could there have been diffuse involvement of the bone marrow by leukemia or a lymphomatous process? An aleukemic leukemia may be manifested by severe pancytopenia. In this particular case there was a great deal of depression of red cells but not much depression of the white cells and platelets. If this was an aleukemic leukemia, I should like to see more earlier forms of white cells in the peripheral blood. There were no forms earlier than 1 late myelocyte, which the laboratory frequently finds anyway. Lymphoma occasionally produces diffuse involvement of the bone marrow, with severe anemia as one of its earliest manifestations. In favor of lymphoma and leukemia is the enlargement of the spleen. However, this enlargement could occur with multiple myeloma or a hemolytic process. It is difficult for me to decide definitely among these diagnoses. Perhaps information about the total protein and albumin-globulin ratio might help. Were they determined?

DR. JACOBSON: No; the electrophoresis was not done either.

DR. SOHIER: The bone marrow, I assume, was! If Dr. Jacobson had entered the marrow and found multiple myeloma, I am sure he would have liked to know what the total protein and albumin-globulin ratio were, and would have ordered them.

I shall say that Dr. Jacobson found many carcinoma cells in the marrow and that probably he could not determine their origin from their appearance. I shall say that the patient had a bronchogenic carcinoma with diffuse invasion of the bone marrow.

DR. ROBERT E. SCULLY: Dr. Colby, have you a comment?

*Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*. 709 pp. Lancaster, Pennsylvania: Lancaster Press, 1931. P. 521.

DR. FLETCHER S. COLBY: I want to compliment Dr. Sohier for summing up the case so well. The significant thing to us was the marked drop in the hemoglobin in a month. We asked Dr. Jacobson to see the patient and to do a bone-marrow aspiration.

DR. JACOBSON: Dr. Colby, did you ever feel a suprapubic mass?

DR. COLBY: No; and I examined the patient the first time under anesthesia.

DR. JACOBSON: The peripheral-blood smear was nondiagnostic. There was a simple chronic anemia, no reactive red cells and a reticulocyte count within normal limits; therefore, it was obvious that a study of the bone-marrow morphology would be the most direct approach to diagnosis.

CLINICAL DIAGNOSIS

Carcinoma, metastatic to bone, ? primary in bladder or prostate.

DR. WILLIAM D. SOHIER'S DIAGNOSIS

Carcinoma, metastatic to bone, ? primary in lung.

ANATOMICAL DIAGNOSES

Recurrent carcinoma of urinary bladder, with metastases to bone, spleen, liver, lungs, and adrenal gland.

Occult adenocarcinoma of prostate.

Bronchopneumonia.

PATHOLOGICAL DISCUSSION

DR. JACOBSON: Under low power the bone marrow revealed a most startling appearance, being practically replaced by large clumps of bluish tumor cells with large anaplastic purple nuclei. Practically no normal myeloid or erythroid cells or megakaryocytes were visible. The cells were three or four times as large as the normal myeloid and erythroid cells. In the Wright stain it is very difficult, if not impossible, to differentiate the various kinds of carcinoma so we sent a generous sample of the clot to the pathologist.

DR. SCULLY: In our paraffin sections there were the same numerous, solid clumps of cells characteristic of undifferentiated carcinoma. We were unable to say more than that the appearance was somewhat more suggestive of an origin from the bladder than from the prostate. The patient was treated with stilbestrol after the diagnosis was made. He died several weeks later. At autopsy there was little in the region of the bladder and prostate that appeared abnormal. The wall of the bladder was edematous and hemorrhagic but contained no obvious tumor. The bones, on the other hand, were extensively replaced by soft tumor. Metastatic disease involved the lumbar and sacral spine, the right clavicle, the one rib that was examined, both ilia and the head of the right femur.

Microscopically, metastases were seen in the spleen, liver, lungs, adrenal glands and regional lymph nodes as well as bone. The bony tumor was composed of cords of undifferentiated epithelial cells that were stimulating osteoid and bone formation. In the bladder, microscopical study showed a few small areas of carcinoma, similar in structure to the metastatic carcinoma and to the bladder cancer resected surgically. In the prostate we found an incidental occult adenocarcinoma, which showed perineural invasion but was well differentiated and looked nothing like the bony tumor.

There was extensive extramedullary hematopoiesis, both liver and spleen containing large numbers of erythroblasts and normoblasts. In the lung sections there were several organizing pulmonary emboli and in the region of the invading capillaries, there were clusters of erythroblasts. This unusual finding can be interpreted as a recapitulation of embryonic development of capillaries and red cells from mesenchyme. There was considerable bronchopneumonia and pulmonary edema terminally.

We sent for the slides from the original operation two years before admission. At that operation a large diverticulum of the bladder, about 10 cm. in diameter, was excised. It was free of tumor. The prostate, removed by the suprapubic route, showed no carcinoma, only benign hypertrophy. The tumor that was resected measured about 3 cm. in diameter and was a papillary type of carcinoma that was poorly differentiated. There was only questionable evidence of invasion at the base. We wondered, in reviewing this case of unusual behavior of bladder cancer, whether or not it is advisable to do a prostatectomy or any other operation on the urinary bladder at the same time that one is treating a carcinoma of the bladder; in other words could the suprapubic prostatectomy and resection of the diverticulum have opened up vascular channels that this very implantable type of carcinoma might have entered? Dr. Colby, would you comment?

DR. COLBY: I think that is a distinct possibility because the tumor is easy to implant and there is very rich circulation in the bladder. It is not very common for a tumor of the bladder and an enlarged prostate to be removed at the same operation.

DR. SCULLY: In your experience how often do carcinomas of the bladder metastasize this widely?

DR. COLBY: The more I see of carcinoma of the bladder, the more unpredictable I learn that it is. I have a patient in the hospital who presented much the same diagnostic problem; he had a large, infected gall bladder that was removed about a month ago, and at that time the entire mesentery was infiltrated with tumor cells from cancer of the bladder.

DR. WILSON: Was there a nodule in the right lung?

DR. SCULLY: There was extensive edema and pneumonia, but no localized lesion was found.

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CARCINOMA OF THE BREAST — ENDOCRINOLOGY AND STATISTICS

IN this issue of the *Journal* the third and final installment of a progress report on carcinoma of the breast is published. The authors' review covers several important aspects of this disease; their treatment cuts across any residual boundaries still lingering between endocrinology and surgery; the importance of accuracy and aggressiveness in radiation therapy is discussed. The responsibility of the doctor who treats this disease is emphasized. The operator who is capable of performing a mastectomy, but knows little else of the disease, had best turn the patient over to someone else or seek competent help from others. The doctor who regards the complex endocrinology of carcinoma of the breast as "just a confusing fog" had best do some reading and studying so that he can find a few landmarks in that fog. As knowledge progresses and discloses new treatments for unfortunate sufferers from this disease, the responsibility of the physician increases because he must encompass new areas of thought and knowledge. Whether or not any of the analytic concepts or therapeutic conclusions expressed by the authors will stand the test of time, no one can say. Before the ink is dry, the entire field may be revolutionized by new endocrine or chemotherapeutic discoveries that pertain either to all of cancer or to carcinoma of the breast alone.

Two aspects of the breast-cancer problem that are mentioned in the review but deserve further editorial emphasis may be discussed briefly. These relate to the delicacies, respectively, of endocrinology in that disease and of the statistical approach to its treatment.

Carcinoma of the breast apparently can be influenced by alterations in the body-fluid concentrations of at least four different endocrine substances: estrogens, androgens, cortisones and growth hormone (or other pituitary factors). Alterations in these concentrations may be produced by the administration of hormones or by the removal of three major glandular areas (gonads, adrenals, pituitary). No other tumor exhibits such a wide range of endocrine influences; carcinoma of the prostate apparently reacts very strongly to alterations in its steroid environment but, according to present evidence, does not respond as well to the removal of the protein hormones of the pituitary by hypophysectomy. This suggests that carcinoma of the breast may be more sensitive to direct stimulation by the pituitary than is carcinoma of the prostate.

If it is true that carcinoma of the breast may grow with increased rate under certain circumstances of increased pituitary activity, there is a potential hazard in the removal of the endocrine "target" glands in this disease: removal of the gonads permits an increased ("unopposed") action of the pituitary as manifested by increased excretion of FSH in the urine. By the same token, adrenalectomy is followed

by increased ACTH secretion; whether there is an associated increase in pituitary breast-stimulating hormone is not known now, but is under study. There are patients in whom the growth of the disease appears to have been accelerated by removal of the steroid-producing glands. "Unopposed" pituitary activity may be at least one explanation of this phenomenon. The surgeon must therefore be prepared to carry out appropriate endocrine and metabolic studies to assess the effects of his surgery on the disease, to avoid harming the patient with his endocrine therapy and to predict — to the limited extent now possible — the effects of his surgery before it is performed. The tumor is responsive, and the endocrine balance a delicate one; harm can be done as well as help given.

Turning to statistics, one finds a spate of papers devoted to the breast-cancer problem. A statistical analysis of the results of treatment is prominent again because of the current controversy over local surgery. Should surgery to the breast be "minimal" (simple mastectomy followed by irradiation), or should it be "maximal" (a radical mastectomy with dissection of the internal mammary and supraclavicular lymph-node chains)? The statistical evidence to settle this point is not yet available. It will take some years to accumulate the necessary data, but, more important than that, it will require careful study employing methods that are statistically valid.

The statistical studies now available in the literature suffer from two main faults. The first is failure to recognize that operative results cannot be compared unless the criteria for patient selection is constant in both series and unless the "entire series" (both treated and untreated) are included. As a gross example to illustrate this point, some years ago a study was made of the natural history of untreated carcinoma of the breast, showing that without any treatment whatsoever about 20 to 25 per cent of these patients were alive at the end of five years. Using that as a background, one can study the results of mastectomy (for example) and, in the treatment of a certain group of cases, find five-year survival rates in the region of 35 to 40 per cent. This appears to be an improvement, but the statistical fault is a glaring one. The "untreated" series has been, statistically speaking, an unselected group of patients since it represents the natural development of a disease process. To contrast it with the effects of radical mastectomy, one must therefore compare it with the survival of *all the patients* suffering from breast cancer and presenting themselves for treatment in the hospital where the mastectomy is being carried out. One cannot compare only those deemed suitable for radical mastectomy with the completely unselected group in the "untreated" cases. Institutions that have denied operation to large groups of patients may show an excellent "five-year survival rate" from their operated cases; yet they may be making very little actual progress with the disease in the population available for treatment. This obvious point, emphasized by many writers on the subject of biostatistics, is often overlooked.

The other fault of many statistical reports in this field lies in failure to use even simple mathematical treatment of the data. Arithmetic cannot make poorly planned studies any better than the data upon which they are based. But arithmetic can help the surgeon to evaluate the significance of differences between truly comparable groups of patients. One of the most hotly contested areas is that contrasting the McWhirter procedure with standard radical mastectomy in patients who present themselves with gross lymph-node metastases. This is one of the most controversial points and one of the most important for solid conclusion. The available information indicates differences in the five-year survival rate of less than 10 per cent. When these differences are subjected to statistical analysis, one finds that they are of very borderline significance with probability values ranging between 0.1 and 0.05. Unless this is candidly admitted by the investigator, the reader may be unaware of the low significance level of these findings.

The studies being carried out by the Tumor Group at the Peter Bent Brigham Hospital may help to give some of the information so sorely needed; their unfolding studies of the various pituitary relations in carcinoma of the breast are very promising. Over a period of many years, the Surgical Service at the Hospital has maintained an interest in the pituitary gland, starting with the work of Dr. Harvey Cushing in 1913 on pituitary tumors and endocrinology, taken up again in terms of the bodily response to stress and injury, and now finding its expression in studies of endocrinology in neoplasia. That little "spit-collecting gland" of Vesalius is still as important as ever, and now its importance is seen in a new setting.

AGE CENTER OF NEW ENGLAND

AGE, the inevitability of which is becoming less obvious to each succeeding generation, will nevertheless always be found on the agenda of life, particularly for that increasing group that now has the time to wait for it. "I do not think," Walt Whitman wrote, "seventy years is the time of a man or woman," nor should any time be set for the ending of the aging process. It is, in fact, inappropriate to speak of the aged, only of the aging; one grows older but never old.

As the span of life has become more and more elastic and the span of man's employment more and more inflexible it has become increasingly imperative to do something more than place arbitrary limits on his usefulness in an organized industrial system. Man can no longer simply and rather childishly "grow old

along with me"; he must have something to do besides holding his own hands or another's in the gloaming.

Efforts at analyzing the problems of senescence are as old as time itself although apparently more successful in early Biblical days than at present. So far as the modern attempt is concerned a notable meeting at the summit took place at the Harvard School of Public Health in the summer of 1954, with discussion revolving around the questions of who and what the aging are, and what their needs may be. Aging as a change that may proceed at varying rates without a chronologic end point was illustrated by a brisk oldster of a hundred and four contrasted with a burned-out metabolic derelict eighty years his junior.

The Age Center of New England, Incorporated, is strategically located in the Hotel Vendome, 166 Commonwealth Avenue, Boston. Now scarcely a year old and hence in the very early stages of its own aging process, it is dedicated to the search for some of the answers to the problems of growing older in the world today. Expressed in careful phraseology it has embarked on the search for those "personality, behavioral and physiological factors" by which successful aging can be scientifically measured — a search so far most successfully prosecuted by the distillers.

Three groups have been influential in the establishment of the Center — physicians with an interest in gerontology; sociologists and psychologists at the university level, similarly interested; and industrial management itself, which, aware of its part in the creation of the situation, is mainly financing the venture. Already over 200 members are registered, their ages ranging from fifty to ninety years, of whom 54 per cent are men and 46 per cent women, generally suffering from social dislocation and the feeling of isolation that accompanies separation from the habits and activities and labors of a lifetime.

Among other things the Age Center is trying to develop technics for predicting the degree to which workers at any level will be disturbed by the marching of the years and the approach of retirement; the forms that an upset, if it occurs, will take, — whether behavioral, psychologic or physical, — and the factors that might prevent or lessen the disturbance. Even as data are gathered for future service to others, service is rendered the participants in helping them to plan for their present or impending retirement; they are helped in an understanding of their problems and a re-evaluation of their lives.

It may be that unionization, with its not altogether fruitless trend toward removing the work from labor, is preparing eligible toilers for the prolonged twilight resulting from a lengthened life and an early retirement; management also is acquiring an increased sense of responsibility for the employed partner in the mutual undertaking that they share. Retirement rules still vary, however, being fixed and inescapable in some industries whereas in others employees are retired selectively according to individual circumstances, and with some there is no retirement except at the request of the employee.

An interesting observation at the Age Center has been the apparently good physical condition of the majority of the members, regardless of age. Needs, which must be met through the co-operation of the medical profession, are for assistance in gathering an adequate staff of voluntary part-time medical and psychiatric workers, and the interest and co-operation of practicing physicians in referring new members and in supplying pertinent information regarding them.

DRUGS WITH DELAYED AND PROLONGED ACTION

THE paper of Feinblatt and Ferguson published elsewhere in this issue of the *Journal* demonstrates the importance of critical re-evaluation by each physician, not only of his own methods but also of the use of new diagnostic and therapeutic tools. Such tools are being developed in increasing numbers by the active pharmaceutical industry, and it is much too easy to accept without question the glowing advertising claims, which are accompanied by reprints and bibliographies to give added authority.

The absorption of drugs by the gastrointestinal tract has always posed a problem. The variations in dosage to obtain the same results in different patients, the individual sensitivities to medicine with real and imagined idiosyncrasies and the varying tolerances and intolerances are well recognized. Are the reasons behind these observations as well established?

The radiologist has observed for years the passage of opaque mediums through the gastrointestinal tract. He has learned that any dogmatic statement of motility time is at best an average figure with wide variations among patients and even at different examinations made upon the same patient. The effect of cold water and of foods in accelerating motility time have been amply described. Many an undissolved pill has been recognized in the colon and rectum, obviously of no value to the patient.

In this age of time bombs and delayed-action fuses, it is not surprising that the pharmaceutical industry should attempt to copy the same pattern with drugs. If this could be accomplished it would simplify the administration of medicines for doctor and patient. A physician's mail is full of printed and pictorial evidence purportedly showing how drugs prepared by patented methods may be fused to be liberated at predetermined intervals and in calculated quantities in the gastrointestinal tract for delayed and prolonged therapeutic action. Increasing use of these products demonstrates how this oversimplification has been accepted by the medical profession. A reinvestigation

of some of the fundamental concepts of gastrointestinal physiology as related to drugs, to discover what procedures can be supported by facts rather than by fancy and habit, is called for. There could be a great difference between disintegration and absorption times, depending on what part of the intestine the drug had reached.

In the article referred to, the authors confirm in the case of the product investigated what radiologists have observed using their diagnostic mixtures: that the gastrointestinal tract tends to disperse material widely and not to pass it through en masse. This contradicts the commercial artist's conception of drug passage but emphasizes that the x-ray method of in vivo study is a good one.

It is hoped that this is just a preliminary study and that the authors will persevere since many variables are present to be assigned relative importance in the digestive process. Filming the subjects at fifteen-minute intervals during the first hour might demonstrate better the rapid dispersal of material in the upper small bowel. The timed capsule could be made up of one timed component only for each trial. Since patients usually have food, the experiment could be performed on nonfasting subjects. The addition of the morning and afternoon coffee breaks and midnight snacks would be optional. The use of radioactive tracers might add further information. Throughout the planning, the carrying out and the interpretation of the experiments, the close association and co-operation of the internist, pharmacologist and radiologist is essential. Such an investigation would go far toward clarifying present concepts of the confusing problem of gastrointestinal absorption. The article may interest others in contributing to that end.

PSITTACOSIS

ATTENTION was recently called in these columns* to the increased occurrence of psittacosis since the relaxation of controls on the interstate shipment of psittacine birds. The growing popularity of such birds, particularly parakeets, as house pets was stressed as a major factor in the resurgence of this disease. Although the incidence of psittacosis may not yet have reached alarming, or even serious, proportions in this country, the recognition of this disease may be greatly enhanced by awareness of its possible presence in relation to exposures to birds, particularly sick ones.

The availability of effective therapy in the tetracycline antibiotics makes the recognition of psittacosis of immediate importance to the patient and his physician. However, as in many diseases that are infrequently encountered, the diagnosis may often be missed or not seriously entertained because of the varied clinical picture, which may simulate other, more common diseases. This point is clearly brought out by the observations on the cases of the disease reported from Cleveland elsewhere in this issue of the *Journal*.

*Editorial. Psittacosis on increase. *New Eng. J. Med.* 253:342, 1955.

Idiots.—*There are 800 idiots in the State of Connecticut, one-fourth of which are under fourteen years of age.*

Boston M. & S. J. *May 22, 1856*

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ECLAMPSIA AND SUBARACHNOID HEMORRHAGE

A thirty-six-year-old gravida VII, para IV, died with eclamptic convulsions and a subarachnoid hemorrhage two weeks before her estimated date of confinement.

The history included 4 term deliveries after two-hour labors that produced babies weighing 3.8 to 4.5 kg. (8½ to 10 pounds). It is categorically stated that there had been no toxemia in any of these pregnancies and no complications. They were her first 4 pregnancies. After 2 miscarriages, a four-year interval preceded the current pregnancy, for which she was examined at two and a half months with a normal blood pressure, negative urinalysis, and weight of 82.1 kg. (181 pounds), her normal nonpregnant weight being 77.1 kg. (170 pounds).

Within a month, the blood pressure had risen to 150 systolic, 90 diastolic, but it did not rise beyond this point for the remainder of her prenatal care, as observed. Weight gain was limited until the seventh month, when she gained 3.6 kg. (8 pounds) in three weeks and showed marked edema. Diamox, salt and fluid restriction and 1 Mercuhydrin suppository weekly resulted in limiting further weight gain to only 0.9 kg. (2 pounds) in the next six weeks. The last prenatal visit was ten days before death with a blood pressure of 130 systolic, 90 diastolic, a weight of 91.6 kg. (202 pounds) — that is, an increase of 13.5 kg. (32 pounds) — and for the first time a + test for albumin. Because there were no subjective toxic symptoms, she was told to return in eight days but failed to do so, entering the hospital in nine days, however, with spontaneously ruptured membranes.

On admission she complained of epigastric distress and was vomiting. The blood pressure was 200 systolic, 130 diastolic; the urine contained 100 mg. of albumin per 100 ml., with rare granular casts in the

sediment. Edema was obvious; the patient seemed anxious, dull and later agitated. The eye grounds showed only venous engorgement. In the absence of labor and with a three-hour history of epigastric distress, she was given simultaneously Luminal Sodium, magnesium sulfate and Pitocin intramuscularly in moderate doses. The 1-minim doses of Pitocin were repeated at half-hour intervals. Within half an hour she was semicomatose, and approximately an hour after admission, labor began but this was associated with a generalized eclamptic convulsion that lasted about five minutes. Additional morphine and magnesium sulfate were given as well as oxygen, but shortly thereafter the uterus failed to relax between contractions. Partial premature separation of the placenta was diagnosed. Adequate doses of morphine and magnesium sulfate, with constant oxygen administration, were continued over the next several hours, but two subsequent convulsions occurred while moderately good labor continued. During the third convulsion, neurologic signs pointed to intracranial hemorrhage. Although the cervix soon became fully dilated, permitting a hasty, easy, low-forceps delivery of a stillborn fetus with minimal bleeding, the patient continued to deteriorate, with blood pressure readings of approximately 210 systolic, 100 diastolic and a pulse rising from 64 to 100. Shortly after delivery, Cheyne–Stokes respirations developed and deepened as she continued in profound coma. For the first time, a flame hemorrhage was now noticed in one optic disk, and the blood pressure fell to abnormally low levels — namely, 64 systolic, 0 diastolic.

A neurosurgical consultation confirmed the diagnosis of subarachnoid hemorrhage, but intervention was obviously contraindicated. She continued to deteriorate further until respirations failed approximately twelve hours later.

This was classified as a preventable death caused by eclampsia and subarachnoid hemorrhage. The primary avoidable factor was delay in hospitalization. Admittedly, these opinions are based on retrospective information, and there is considerable doubt about the patient's outlook if hospitalization and vigorous treatment had been instituted several days or even a week earlier. However, she was known to be overweight at the beginning of her pregnancy; the diastolic-pressure readings were consistently 90 or over, and there had been sufficient sudden weight gain to warrant the administration of Diamox and Mercuhydrin. This means that she was a recognized candidate for pre-eclampsia. Under the circumstances, particularly since albuminuria had become apparent, her prenatal visits should have been made every two to four days after the 3.6-kg. (8-pound) weight gain instead of which an eight-day interval was permitted. The conscientious use of Diamox and Mercuhydrin had achieved some diminution in the edema, but there is now some opinion that these agents may mask the severity of pre-eclampsia in women who use them with good effect — that is, the edema, which is a sign of the pathologic process, can be artificially diminished, yielding a false sense of security. Perhaps this explains the eight-day interval. The patient herself was to blame for failing to keep even this appointment, and it is perhaps fortunate that spontaneous rupture of the membranes forced her to the hospital. In responsibility for this death, the physician and patient both must share a portion.

After admission, the story seems to have been one of prompt, vigorous and intelligent measures directed in vain at a process that had already become too far advanced for solution. Surprisingly enough, the urine on admission contained only 100 mg. of albumin per 100 ml. Presumably, the kidneys may have almost ceased functioning, and the urine obtained by catheter may have been resting in the bladder for some time. Since the urine collected after delivery contained such a small amount of albumin, one must assume that the terminal event was primarily due to intracranial hemorrhage rather than the eclamptic process per se and, therefore, that the patient's doom was sealed during her third convulsion when subarachnoid hemorrhage occurred.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATHS

LAWRENCE — Joseph H. Lawrence, M.D., of Brockton, died on April 19. He was in his eighty-sixth year.

Dr. Lawrence received his degree from Bellevue Hospital Medical College in 1892. He was a member of the staff of Brockton Hospital for thirty-five years and served twelve years on the Board of Health.

He is survived by two daughters.

MANDEVILLE — Ernest A. Mandeville, M.D., of Holyoke, died on January 26. He was in his sixty-second year.

Dr. Mandeville received his degree from Tufts College Medical School in 1919.

He is survived by his widow and a son.

CORRESPONDENCE

MIRACULOUS CRUET

To the Editor: Regarding the "value of cider as a prophylactic of cholera" in the February 7, 1856, issue of the *Journal*, I should like to report some observations I have made in the medical literature on fully fermented cider vinegar.

In the *Landmark of Medicine; Laity lectures of the Academy of Science*, introduced by James Alexander Mitter, M.D., 1935, one reads: "Bartholomew, the Englishman wrote on Medicine in the encyclopedia which he wrote under the title 'Principle of Things', 'In case of bad breath, the gums shall be washed with warm vinegar.'"

In the history of the death of George Washington, given by the physicians who attended him during the illness that proved fatal, one finds: "Vapours of vinegar and of water were frequently inhaled" and "blisters were applied to the extremities, together with a cataplasm of bran and vinegar to the throat."

Sir Edwin Lankester, M.D., LL.D., in his *"Practical Physiology,* writes: "From recent chemical researches it appears

that volatile oils which give odor to plants or other bodies of similar nature such as camphore have a power of destroying animal poisons. It is in the belief of this kind that has lead to employment of strong smelling compounds, such as 'aromatic vinegar' as a means of preventing the spread of contagious disease."

Samuel Marewood, Esq., collector of excise in Dublin, in his book, *A Philosophical and Statistical History of the Inventions and Customs of Ancient and Modern Nations in the Manufacturing and the Use of Inebriating Liquors*, (1838): "The bad effects of belladona are most powerfully prevented by a glass of warm vinegar" and, again, "any man leaving the use of opium requires some substances or stimulants. Dr. Aliston narrates in Edinburgh Essay, 'opium addicts to stop were given to drink wine and wine cured.'"

Karl J. Karnaky, M.D., reported in a letter to the editor of the *Journal of the American Medical Association* (**157**: 1155, 1955), on the use of vinegar that he has made in trichomonas vaginalis stating that he "was the first person to write about vinegar douche in the American medical literature."

An article in *Current Medical Digest* (March, 1951) on vinegar as antibiotic states: "The use of vinegar in medicine dates back to antiquity. Beyond doubt vinegar is the first antibiotic known to man, a bacterial product antagonistic to other organisms." It mentions a topical use of vinegar in the ear and as a wet dressing on wounds, and with chronic middle-ear infection by I. L. Ochs (*Arch. Otolaryng.* **52**:935-941, 1950).

EMANUEL ANASTESSOFF, M.A.
Milton, Massachusetts

BOOK REVIEWS

Transplantation of Tissues: Cartilage, bone, fascia, tendon, and muscle. By Lyndon A. Peer, M.D. 4°, cloth, 421 pp., with 163 illustrations. Baltimore: The Williams and Wilkins Company, 1955. $13.50.

This book covers the subject of transplantation of tissues, which has become a fast developing field of surgery. Dr. Peer's book not only opens the door to this very interesting subject but also presents it with clarity and impartiality. The scope of this field is realized when the subject is discussed from microdissection and microtransplantation of cells to the clinical transplantation of tissues such as cartilage and skin in plastic surgery; tendons, fascia, muscles and bone in orthopedic surgery; and blood vessels in vascular surgery.

Dr. Peer presents the first volume in 421 pages divided into six main sections, including cartilage, bone, fascia, tendons and muscles. In each section experimental work in tissue transplantation in animals is first presented and is followed by clinical experience in human beings.

Controversial subjects are thoroughly discussed, and conclusions are carefully evaluated. Dr. Peer's unbiased approach is well summarized in his own words:

> Although many of the factual findings in this book may be accurate, about 50 per cent of the interpretations and conclusions will probably be wrong. These erroneous conclusions will be exposed by future investigators, and our knowledge regarding the behavior of free tissue grafts advanced.

CARTER R. ROWE, M.D.

Basic Surgical Skills: A manual with appropriate exercises. By Robert Tauber, M.D. 4°, cloth, 75 pp., with 51 illustrations. Philadelphia: W. B. Saunders Company, 1955. $3.75.

A valuable contribution to the training of the surgeon. Every medical student should contemplate these basic technical factors seriously. Those who are undecided regarding the type of practice they will eventually pursue will not be harmed by these details of sutures and surgical knots, regardless of their ultimate specialty.

Interns and junior surgical residents can benefit tremendously by the outline of study and daily practice with these simple and well illustrated maneuvers. Valuable time can thereby be saved in the early days in the operating room.

The author goes into great detail to reveal every step of a technic that he has found successful. Even though it strongly emphasizes the procedures as applied to gynecology, the book offers general principles that will be found useful in any surgical field.

ARTHUR W. ALLEN, M.D.

Pathology. By Peter A. Herbut, M.D. 8°, cloth, 1227 pp., with 1378 illustrations. Philadelphia: Lea and Febiger, 1955. $16.00.

The author, who is professor of pathology at Jefferson Medical College, has undertaken to write a textbook simple enough for beginners and at the same time sufficiently broad in scope to appeal to postgraduate students of medicine. The product, unhappily, is not ideally suited to the needs of either class of reader.

There are, in my opinion, two basic faults in this work: an overly didactic approach, and a lack of balance in the treatment of the subject matter.

Regarding the first criticism, the style is telegraphic and unadorned—so much so that the reader can hardly avoid the unpleasant sensation that he is preparing for an examination. He is continually encountering lists of items numbered from 1 to 5 or even 10. These do not make for easy reading, nor are the most significant facts or items always properly highlighted by this mode of presentation. Moreover, there is a tendency to oversimplify complex pathologic processes and to offer gratuitous interpretations of them. Although this may delight second-year students, it will undoubtedly disappoint experienced readers, who prefer a more complete presentation of facts to document an author's opinions.

Despite the encyclopedic character of the book (this, in itself, lessens its value to beginners), there is a lack of perspective in that a number of important disorders receive but cursory mention. For example, there is no discussion of pulmonary edema or of chronic valvular disease of the heart. Although there are seventeen lines on hypertrophy of the uterus, only one or two appear on carcinoma-in-situ of the cervix, a subject of considerably greater moment. The information presented on post-traumatic renal insufficiency and other forms of renal tubular necrosis is sketchy. Aside from specific omissions, pathogenesis and pathophysiology in general receive too little emphasis at the expense of inclusion of much that is rare and exotic.

The illustrations, like the text, are uneven. Many are excellent. A few are so poor, on the other hand, that it is difficult to identify the lesion even after one has read the caption. The color plates are not of uniformly high quality.

Despite its shortcomings, Dr. Herbut's book has merit. Between its cover is a considerable amount of factual detail not to be found in other textbooks. The presentation of the subject matter is straightforward, orderly and uniform from chapter to chapter. The discussion of each major pathologic entity includes a consideration of its clinical aspects. This, even though little more than outline in form, serves to emphasize to students the prominent place of pathology in the total medical picture.

ROBERT E. SCULLY, M.D.

Reflections on Renal Functions. By James R. Robinson, M.D., Ph.D. 8°, cloth, 163 pp. Springfield: Charles C Thomas, 1955. $3.50.

This book is based on a series of lectures given by the author to classes in physiology in the University of Cambridge, England. The chapters dealing with glomerular filtration and tubular reabsorption, tubular secretion, excretion of water and sodium, renal control of acid-base balance, regulation of renal function and regulation of the volume of the body fluids are critically and interestingly presented. The author offers "a clear picture without concealing its incompleteness and lack of finality." This book of 163 pages and 112 references will be of value to those who require a brief summary of renal physiology and do not have the time to explore the extensive literature of the field.

HARRY A. DEROW, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cardiovascular Surgery: Studies in physiology, diagnosis and techniques. Proceedings of the Symposium Held at Henry Ford Hospital, Detroit, Michigan; March, 1955. Edited by Conrad R. Lam, M.D., surgeon-in-charge, Division of Thoracic Surgery, Henry Ford Hospital. 4°, cloth, 543 pp., with illustrations and tables. Philadelphia: W. B. Saunders Company, 1955. $12.75.

Recent Advances in Neurology and Neuropsychiatry. By Sir Russell Brain, Bt., D.M. (Oxon.), P.R.C.P., physician to the London Hospital, and the Maida Vale Hospital for Nervous Diseases; and E. B. Strauss, M.A., D.M. (Oxon.), D.Sc., F.R.C.P., physician for psychologic medicine, St. Bartholomew's Hospital. With the assistance of Denis Hill, M.B., F.R.C.P., D.P.M.; Douglas Northfield, M.S., F.R.C.S.; and David Sutton, M.D., M.R.C.P., F.F.R., D.M.R.D. Sixth edition. 8°, cloth, 311 pp., with 46 illustrations and 1 table. Boston: Little, Brown and Company, 1955. $7.50.

Surgery of the Heart. By Charles P. Bailey, M.D., M.Sc. (Med.), LL.D. (Hon.), F.A.C.S., F.C.C.P., F.I.C.S., professor of thoracic surgery and head, Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, director of thoracic surgery, Deborah Sanatorium, Browns Mills, New Jersey, director, Bailey Thoracic Clinic, Philadelphia, and thoracic surgeon, Doctor's Hospital, Incorporated, Philadelphia, Abington Memorial Hospital, Abington, Pennsylvania, Philadelphia General Hospital and United States Veterans Administration Hospital, Philadelphia. 8°, cloth, 1062 pp., with 1452 illustrations, 3 color plates, and 45 tables. Philadelphia: Lea and Febiger, 1955. $25.00.

Wiederherstellung der Lebenstüchtigkeit geschädigter Menschen: Rehabilitation in inländischer und ausländischer Sicht. By Dr. med. habil. Hans Hoske, Köln. 8°, paper, 217 pp. Stuttgart: Georg Thieme, 1955. $3.80. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Group Processes: Transactions of the First Conference, September 26, 27, 28, 29, and 30, 1954. Ithaca, New York. Edited by Bertram Schaffner, M.D., University Seminar on Communications, Columbia University, New York. 8°, cloth, 334 pp., with 40 illustrations. New York: Sponsored by the Josiah Macy, Jr., Foundation, 1955. $5.50.

Handbook of Toxicology: Acute toxicities of solids, liquids and gases to laboratory animals. Edited by William S. Spector. 4°, paper, 408 pp. Philadelphia: W. B. Saunders Company, 1956. $7.00. (Prepared under the direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences, and National Research Council.)

Diseases of the Liver. Edited by Leon Schiff, M.D., Ph.D., professor of clinical medicine, University of Cincinnati College of Medicine, and director, Gastric Laboratory, Cincinnati General Hospital. With a foreword by Cecil J. Watson, M.D., Ph.D. 4°, cloth, 738 pp., with 244 illustrations and 44 tables. Philadelphia: J. B. Lippincott Company, 1956. $16.00.

Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and host: With an addendum on leprosy. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Margaret P. Cameron, M.A., A.B.L.S.; assisted by Cecilia M. O'Connor, B.Sc. 8°, cloth, 396 pp., with illustrations and tables. Boston: Little, Brown and Company, 1955. $9.00.

Practitioners' Conferences: Held at the New York Hospital–Cornell Medical Center. Vol. 3. Edited by Claude E. Forkner, M.D., professor of clinical medicine, Cornell University Medical College, attending physician, New York Hospital, and consultant in medicine (hematology), Roosevelt Hospital. 8°, cloth, 293 pp., with illustrations. New York: Appleton-Century-Crofts, Incorporated, 1956. $6.75.

Postural Back Pain. By Milton C. Cobey, M.D., professor of orthopedic surgery, Georgetown University School of Medicine. 8°, paper, 78 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1956. $3.00. (Publication No. 280, *American Lecture Series.*)

Psychopathology of Childhood. Edited by Paul H. Hoch, M.D., New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons; and Joseph Zubin, Ph.D., New York State Psychiatric Institute and Department of Psychology, Columbia University. 8°, cloth, 303 pp., with illustrations, tables and a frontispiece. New York: Grune and Stratton, 1955. $6.00. (Proceedings of the forty-fourth annual meeting of the American Psychopathological Association, held in New York City in June, 1954.)

Roentgen Interpretation of Fractures and Dislocations. By Joseph Levitin, M.D., chief, Department of Radiology, Mount Zion Hospital, San Francisco; and Ben Colloff, M.D., associate chief, Department of Orthopedic Surgery, Mount Zion Hospital, San Francisco. 8°, cloth, 265 pp., with 258 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $7.75.

Shock and Circulatory Homeostasis: Transactions of the Fourth Conference, December 6, 7, and 8, 1954, Princeton, New Jersey. Edited by Harold D. Green, M. D., professor of physiology and pharmacology, and associate in internal medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 8°, cloth, 291 pp., with 69 illustrations and 26 tables. New York: Josiah Macy, Jr., Foundation, 1955. $5.00.

Diseases of the Endocrine Glands. By Louis J. Soffer, M.D., clinical professor of medicine, State University of New York College of Medicine, New York City, and attending physician and head of endocrinology, Mount Sinai Hospital, New York City. Second edition, thoroughly revised. 8°, cloth, 1032 pp., with 102 illustrations, 28 tables and 3 colored plates. Philadelphia: Lea and Febiger, 1956. $16.50.

Fractures of the Facial Skeleton. By N. L. Rowe, F.D.S.R.C.S. (Eng.), L.R.C.P. (Lond.), M.R.C.S. (Eng.), L.M.S.S.A. (Lond.), H.D.D.R.C.S. (Edin.), consultant in oral surgery, Plastic and Maxillo-facial Surgery Unit, Rooksdown House, Basingstoke, Hants, and civilian consultant dental surgeon to the Royal Navy; and H. C. Killey, F.D.S.R.C.S. (Eng.), L.R.C.P. (Lond.), M.R.C.S. (Eng.), L.M.S.S.A. (Lond.), H.D.D.R.C.S. (Edin.), consultant in oral surgery, Plastic and Maxillo-facial Surgery Unit, Rooksdown House, Basingstoke, Hants. With a foreword by Sir Reginald Watson-Jones, B.Sc., M.Ch.Orth., F.R.C.S., F.R.A.C.S. (Hon.), F.A.C.S. (Hon.). 4°, cloth, 923 pp., with 1231 illustrations. Baltimore: The Williams and Wilkins Company, 1955. $22.00.

A Course in Practical Therapeutics. By Martin Emil Rehfuss, M.D., professor of clinical medicine, emeritus, and director of the Division of Therapeutics in the Department of Medicine, Jefferson Medical College, and attending physician, Jefferson Medical College Hospital, Philadelphia; and Alison Howe Price, M.D., associate professor of medicine, Jefferson Medical College, assistant physician, Jefferson Medical College Hospital, Philadelphia, and chief clinical assistant, Diabetic Clinic, Curtis Clinic, Philadelphia. Third edition. 4°, cloth, 972 pp., with illustrations and tables. Baltimore: The Williams and Wilkins Company, 1956. $15.00.

Diagnosis and Treatment of Vascular Disorders (Angiology). Edited by Saul S. Samuels, A.M., M.D., editor-in-chief, *Angiology,* president, Angiology Research Foundation, director of angiology and attending vascular surgeon, Brooklyn Hebrew Home and Hospital for the Aged, chief, Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, consulting vascular surgeon, Long Beach Memorial Hospital, Long Beach, New York, and president, American College of Angiology. 4°, cloth, 621 pp., with illustrations and tables. Baltimore: The Williams and Wilkins Company, 1956. $16.00.

NONCLINICAL NOTES

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The Lemuel Shattuck Medal of the Massachusetts Public Health Association was awarded on April 24 to Dr. Alton S. Pope, former director of the Division of Tuberculosis and deputy commissioner of the Massachusetts Department of Public Health. At the same meeting Dr. Alfred L. Frechette, director of the health division of the United Community Services of Boston, was elected president of the Association.

LOCAL BOYS MAKE GOOD

Boston seems to have been in the front row at the recent annual meeting of the American Psychiatric Association in Chicago. Dr. Harry C. Solomon, professor of psychiatry and chairman of the Department of Psychiatry at Harvard Medical School and medical director of the Boston Psychopathic Hospital, who has never been analyzed, was chosen president-elect; Dr. Jack Ewalt, Commissioner of Mental Health of the Commonwealth of Massachusetts was elected treasurer; and Dr. William Malamud, professor of psychiatry at Boston University School of Medicine, was elected secretary.

NOTICES

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Massachusetts Society of Anesthesiologists will be held at the Harvard Club of Boston, 374 Commonwealth Avenue, on Friday, June 1, at 7:30 p.m. Dr. Nicholas Greene will give a talk entitled "After Eight Years: The present status of induced hypotension."

NEW ENGLAND HOSPITAL STAFF CLINICAL CONFERENCE

A meeting of the New England Hospital Staff Clinical Conference will be held in the Nurses' Home, New England Hospital, Columbus Avenue and Dimock Street, Roxbury, on Thursday, June 7, at 8 p.m. Dr. Grantley W. Taylor will talk on the subject "Cancer of the Breast." All physicians are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

May 18. New England Rheumatism Society. Page 875, issue of May 3.
May 18–29. Consultation Clinics for Crippled Children in Massachusetts. Page 819, issue of April 26.
May 22–24. Massachusetts Medical Society Annual Meeting. Page 868, issue of May 3.
May 23. Boston Branch. American Medical Women's Association. Page 773, issue of April 19.
May 28. Jewish Memorial Hospital. Page 924, issue of May 10.
May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.
May 29. Boston City Hospital House Officers' Association. Page 924, issue of May 10.
June 1. Massachusetts Society of Anesthesiologists. Notice above.
June 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.
June 4–6. Third National Cancer Conference. Page 876, issue of May 3.
June 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
June 6–10. American College of Chest Physicians. Page 876, issue of May 3.
June 7. New England Hospital Staff Clinical Conference. Notice above.
June 9 and 10. Society for Investigative Dermatology. Page 876, issue of May 3.
June 10 and 11. American Gastroscopic Society. Page 875, issue of May 3.
June 15. New England Pediatric Society. Page 924, issue of May 10.
June 17. American Electroencephalographic Society. Page 924, issue of May 10.
June 18–20. American Neurological Association. Page 875, issue of May 3.
June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
June 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 24

THURSDAY, MAY 24
Massachusetts Medical Society Meeting. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Guest Speaker of the Bingham Associates. Disturbances in Potassium Metabolism. Dr. Gerald D. Aronsen. Cape Cod Hospital, 27 Park Street, Hyannis.
*11:00 a.m.–12:00 m. Pediatric Conference, Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Topics in Congenital Heart Diseases. Dr. Leonard S. Sommers. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Lectures for Residents by Medical Division of the General Staff. Anuria. Dr. George E. MacDonald. Private Dining Room, New England Deaconess Hospital.
*3:00 p.m. Thoracic Conference. Esophageal Lesions. Dr. Alexander S. MacMillan, Jr. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, MAY 25
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Pineal—Gland or Vestige? Dr. Julian Kitay. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham presiding. Auditorium, Carney Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Orthopedic Clinic. Mount Auburn Hospital, Cambridge.

(Concluded on page xxvi)